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Milestones in Malaria

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Although an accurate knowledge of the intricacies of the malaria parasite is essential to the protozoologist, nevertheless some acquaintance with the high spots of recent research upon this subject is desirable for the practical physician. Nay further, it may be claimed that without some appreciation of these advances he is not in a position to treat his malaria-stricken patients scientifically or with confidence. In what way are these advances so important? Surely it may be claimed that of all the classical diseases our knowledge of malaria is the most intimate and complete. But this complaisance is soon shattered by recent happenings and by the most important and fundamental discoveries since the demonstration of the malaria parasite itself by Laveran in 1880.

For over 30 years the dictum of F. Schaudinn in 1902 that the sporozoite (or infecting form) liberated from the salivary glands of the mosquito enters the red blood corpuscle and thus initiates the cycle of the malaria parasite in the blood has held the field. Schaudinn claimed to have seen the process with his own eyes and from that time on his diagrams have furnished the basis of the life cycle of the malaria parasite in textbooks. No one dared to doubt the unquestioned authority of such a great man. But there were disquieting features. Many had tried to repeat Schaudinn's experiments and had failed.

Soon, however, with the advent of Wagner-Jauregg and the introduction of his malarial pyrotherapy, a much more intimate study of malaria became possible. By 1924 it was noted by W. Yorke and J. W. S. Mache that this artificially-induced malaria differed from the naturally acquired disease in some important respects. The incubation period (or the intrinsic period of primary development in the human host) was reduced from 8-10 to 1-3 days, and, more remarkable still, it was found possible, indeed easy, to reduce the fever, banish the parasite and prevent relapses in therapeutic malaria produced by direct blood inoculation with minute doses of quinine whilst the mosquito-produced fever behaved like the ntaurally-acquired disease and proved more intractable to quinine and more prone to produce numerous relapses. These anomalies could only be explained, as S. P. James insisted during the next decade, by the asumption that the sporozoite, on entry into the blood, underwent a preliminary development in some other organ before entering the bloodstream. In the meantime, malariologists in Britain, America, Germany and India had turned to a study of the malaria-like parasites of birds and monkeys which behaved in many ways like the human malaria parasites and are amenable to the same drug. Notably this was done in Germany by Roehl and Kikuth in their production of plasmoquine, atabrine and other antimalarial drugs.

In 1936-1937 Raffaele in Italy, Kikuth and Mudrow in Germany showed that in infected canaries tissue-invading forms of the parasites *(Plasmodium cathemerium* and *P. praecox,* or *P. relictum)* were to be found in various organs of the body whither they were carried by macrophage cells into which the sporozoites had penetrated in the first instance, but the most complete demonstration was by S. P. James and P. Tate in 1937 in *Plasmodium gallinaceum,* a parasite of fowls which closely resembles the human plasmodium. These discoveries with this parasite were continued in 1943 by Reichenow and Mudrow in Germany and in 1944 by Huff and Coulston in America. At this stage a short period ensued in which all further attempts to find the hypothetic exo-erythrocytic stage were foiled. The next ray of light came from an unexpected quarter. In 1947 exo-erythrocytic stages were demonstrated for the first time in mammalian malaria by Mer and

Goldblum in the liver of a bat infected with the plasmodium peculiar to these creatures and still more exciting was the description by P. C. C. Garnham in Kenya of small cysts full of tissue-developing forms in the liver of monkeys infected with *Plasmodium kochi.* The difficulty of acceptance of the theory here lay in the fact that this particular parasite differs in some important respects from the human plasmodium and should therefore be included in the genus *Hepatocystes.* Soon, however, the clouds of doubt were rolled away by Shortt, Garnham, Shute and Malamos working on *P. cynomolgi,* a monkey parasite which is closely related to the benign human parasite—*Plasmodium vivax,* and in causing an immense infection by using a large number of plasmodium-infected mosquitoes, they discovered in the liver numerous large parasites, 26-30μ in diameter, some seven days after the primary infection. These resembled in staining reactions the tissue forms of bird malaria already described.

In 1945 the quite remarkable and fundamental researches of N. H. Fairley and associates in Cairns, Queensland, were published. From the facts which emerged the only logical deduction was that a similar development took place in man. These experiments, which were on an unprecedented scale, differed from all others in that human volunteers were employed. These were non-immune soldiers who submitted themselves to bites by infected anopheles and also to the production of malaria by direct blood inoculation. By these means a remarkable fact was revealed. If such a volunteer were bitten on one arm the sporozoites could be recovered from the blood of the opposite member for seven minutes only and were capable of infecting another individual, but after this short period they disappeared, in the case of the benign tertian, for eight days. The question arose where had they gone in the meantime? The answer was that they were probably hidden in the deeper recesses of some solid organ. Anyhow, the solving of the problem seemed unescapable. Finally with all this mass of suggestion and evidence behind them Shortt, Garnham and Malamos in the early month of this year have put the seal on this great work, again by the use of a human volunteer. They were so fortunate as to find an individual who suffering from general paresis had been treated with malarial pyrotherapy and had been considerably benefitted thereby some 2 years previously. He consented to be infected by a massive dose (16 million sporozoites) which was derived from over 2000 infected anopheles as well as by the intravenous injection of sporozoites from the salivary glands of 200 others. With such an immense infection it might have been supposed that the patient would have become dangerously ill; that he might even have died. But such gloomy prognostications misfired entirely. He continued in good health and manifested no signs of malaise or fever. On the seventh day he was subjected to an anaesthetic and a piece of his liver was removed by biopsy. The patient remained well and has never developed malaria since nor have malaria parasites been demonstrated in his blood. The liver sections of this case were most successful. There plasmodial masses were easily demonstrated inside the hepatic parenchyma cells. Some of them (on the seventh day) showed that the schizont was full of segmenting bodies (or cryptomerozoites) and some of these were escaping from the cyst and entering an adjacent blood capillary. This would indicate that at this stage a blood infection with the entry of these cryptomerozoites into the blood corpuscles takes place so that an attack of malarial fever could be anticipated, but this did not occur. Why? The answer is that a very active immunity to malarial infection is produced in the bloodstream and in such an immune subject the merozoites are killed by the immune bodies in the serum and subsequently devoured by leukocytes. This immune body must be of great potency and, if it could be isolated, would prove of great value in the production of passive immunity in those exposed to malaria. Round-cell infiltration of the liver takes place at the site of the destroyed plasmodial masses and these changes may well explain the gross tissue

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Intravenous Quinine in Post-war Malaria

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This study covers 271 cases of chronic malaria treated during the past two years. They include 259 cases of civilian population that have a chronic malaria and twelve ex-service men who developed their malaria while in the service overseas. The acute cases treated during this period of time have been excluded from this study, even though many of them have taken intravenous quinine, because the authors were interested primarily in chronic malaria. In this study no attempt has been made to identify the type of organisms though it is felt that most of them are of the benign tertian or tertian type and the diagnosis of malaria was made largely from the history, symptoms, and physical examination and other blood studies. Most of the patients had a leukopenia and high small lymphocyte count even though the *Plasmodium vivax* was not found in either the thick or thin smears. The authors have found it very difficult in their practice to identify the parasites in chronic malaria. The frequent change of technicians has contributed to this in no small degree. There was practically a universal enlargement of the spleen and tenderness of that organ.

The study was carried out in a general practice in Louisiana which is largely representative of the general population. The cases reported are only those treated within the last two years and in no way can be called a comprehensive study of chronic malaria.

From the Sanders Clinic. Read before the National Malaria Society and the American Society of Tropical Medicine meeting conjointly, December 4, 1947, at Atlanta, Georgia.

Previous Studies on Malaria

All references to previous work refer to J. P. Sanders. J. C. Sanders is appearing for the first time in the American Malaria Literature.

In previous publications the author reported considerable work done on cinchona alkaloids which included quinidine, quinine, cinchonine, cinchonidine and other rare cinchona alkaloids.[1, 2, 3, 4, 5, 6]

Previous work indicated that 25 to 40 per cent of all the acute cases of malaria went into the chronic phase.[4, 7] Chronic cases of malaria tend to relapse year after year with acute exacerbations from time to time, gradually lessening in severity and intensity as the element of time increases. All the anti-malaria drugs used seemed to have about the same value in relieving the acute attack and preventing a recurrence. It was felt that there was some advantage in the change of drugs though the 25 to 40 per cent usually went on into a chronic malaria. Reinfections could not be ruled out since the patient was treated in his native habitat and was subject to the same environment that caused him to get his malaria the first time. This seemed to be an advantage rather than a disadvantage

TABLE 1

AGE	COLOR		SEX		TOTAL
	WHITE	COLORED	MALE	FEMALE	
Under 20	16	6	8	14	22
21-30	43	6	9	40	49
31-40	51	6	18	39	57
41-50	52	8	25	35	60
Over 50	63	8	22	49	71
Total	225	34	82	177	259

since it indicated what one might expect in a "normally" malarial district.

The mortality was high in the first two or three years of life but gradually subsided so that there was practically no mortality among grown-ups. The author gradually developed the opinion that the majority of all the people in this area develop malaria sooner or later and probably have some immunity to it.

Earlier many individuals, DeLee,[8] the author and others, indicated that intravenous quinine for acute malaria was very efficacious. The patient was relieved quickly, the mortality rate was reduced and the patient was soon returned to normality.

The Present Work

Since intravenous quinine with glucose had worked so well with acute malaria, we began to try it on chronic cases, patients that relapsed from time to time. The results were very good.

The method of administration included five to fifteen grains of quinine dihydrochloride in 1000 cc. of 5 or 10 per cent glucose. The usual dose was ten grains of quinine. The infusion was repeated usually within two or three days though an occasional case got an infusion every day. As his symptoms improved, the interval between infusions was gradually increased so that some patients got an infusion only every seven days. The patient's well-being as determined by his own reaction and that of the physician was the determining factor for the number that he got and the interval between infusions. No pattern was set to be followed in very case.

The Chronicity of these Cases

167 out of 259 cases (64 per cent) (table 2) admitted that they had had from one to six or more attacks before treatment was started. Leading questions in the history taking probably would have revealed more. This series represents 225 white people and only 34 colored (table 1). This is in contrast to previous reports made by the author when he was practicing at Caspiana, Louisiana, where the population was largely colored. For the most part the patients are well housed, well nourished, homes are well screened and the patients are well cared for medically. They represent every stratum of society from the richest to the poorest, though there are few of the latter in this series. In previous work there were by far the greater number in the low income bracket. Most of this series were adults, 237 out of 259 (table 1), and over half, 131 out of 259, were past forty years old, the largest group being past fifty.

We were able to identify parasites in the blood at one time or another in only 72 cases (28 per cent) though thick and thin smears were made on every patient and were made on some patients many times.

Symptoms and History

Histories of previous attacks were listed in 167 cases (64 per cent) though leading questions were usually avoided. The ailments usually included almost every symptom of any disease known to man. However, chills and fever were much less frequent than is seen in acute malaria. It was only in acute exacerbations that chills

TABLE 2

PREVIOUS ATTACKS REPORTED

Color & Sex	1	2	3	4	5	6 or More	
White Male	12	13	4	2	0	2	
White Female	50	38	18	1	2	2	
Colored Male	4	4	0	0	0	0	
Colored Female	6	9	0	0	0	0	
Total	72	64	22	3	2	4	167

TABLE 3

TOTAL NUMBER OF INFUSIONS GIVEN

Color & Sex	1	2	3	4	5	6	7	8	9	10	11	12	Over 12	Total Patients
White Male	9	17	10	15	3	1	2	3	2	2	1	1	1	67
White Female	23	33	31	25	15	8	7	8	3	1	2	0	2	158
Colored Male	5	1	4	2	1	2	0	0	0	0	0	0	0	15
Colored Female	4	5	3	5	2	0	0	0	0	0	0	0	0	19
Total	41	56	48	47	21	11	9	11	5	3	3	1	3	259

were present at all and they varied all the way from shaking chills to "dumb" chills. Headache was the most prominent symptom and was prevalent in almost every case. Then followed: aching all over, joint pain, subnormal temperature, loss of appetite, loss of weight, nosebleed, hematuria, blood in stools, lowered blood pressure and many other symptoms too numerous to mention. Many cases of cough that resisted treatment and were x-rayed for tuberculosis were found to have chronic malaria and after treatment was instituted the cough promptly subsided. Gastro-intestinal symptoms suggestive of gallbladder or gastro-intestinal disease were apparent in some cases and cardiac pain was seen in others.

Results of Intravenous Quinine in this Series

No attempt was made to control the number of infusions given any one patient. We stopped when the patient had improved sufficiently and this was decided entirely by the doctor and the patient himself. However, three to five infusions at two to three day intervals was usually sufficient to control an attack (table 3). Occasionally one infusion was sufficient and also occasionally it was necessary to give seven to ten to completely relieve the patient of all his symptoms. It will be noted that 192 stopped after four infusions and 213 stopped with five which illustrates the efficacy of that number (able 3). The number of infusions in this table indicated all infusions given each patient including his relapses.

The three cases (table 3) that have taken more than twelve were two women and one man. The man has taken thirty and the two women about forty each. All of them have been found to have parasites on numerous occasions and were temporarily relieved after each set of about three. One woman, aged 68, has no other complications but the other two have some chest complications that may be causing their fever. Both have had fever for over two years.

Only 56 (22 per cent) (table 4) have reported relapses since the first infusion was taken but this is only a two year study

TABLE 4

NUMBER OF ATTACKS AFTER FIRST INFUSION

Color & Sex	1	2	3	4	5	6	Total
White Male	10	2	0	0	0	2	14
White Female	32	3	2	0	0	2	39
Colored Male	2	0	0	0	0	0	2
Colored Female	1	0	0	0	0	0	2
Total	45	5	2	0	0	4	56

and, consequently, cannot be construed as the relapse rate. Other medication has been taken at the same time by mouth concurrently with the infusions (table 6). It will be noted that this includes all the common anti-malarials now used: quinine, quinidine, totaquine, atabrine and aralen. While some of these patients are evidently well and will have no more relapses, most of them are expected to have recurrences sooner or later. I have one patient not included in this list that had a benign tertian infection, the same one, for seventeen years. He has now been free of malaria or at least has taken no treatment for the past three years and we hope that he is well.

There are a few bad effects from intraveneous quinine but usually they are not disturbing. Occasionally the patient has some shock, may have a chill and a low grade of temperature. There is considerable nausea and nervousness in other patients and a few patients have been definitely allergic to the quinine and medication had to be stopped or the infusion discontinued. It might be said in this connection that one or two patients that have been allergic to quinine by mouth have been able to tolerate it as an infusion. For example, the authors had a patient who was almost killed twenty years ago with intravenous quinine by syringe who takes it now as an infusion without any apparent difficulty. We are not sure that this is his original infection of twenty years duration or a new infection that has developed in the past three years. He had a period of about ten or twelve years in which he thought he was clear of the infection.

Service Men's Record

This group included twelve men who saw service in World War II, eleven white and one colored, all males. Eight of them were in their 20's and four in their 30's. Eight contracted their malaria in the South Pacific, one in North Africa, one in Europe, one in Central America and one in the United States. All of these were Louisiana boys who, in my opinion, had developed some immunity before they went into the service. Most of them had taken atabrine, particularly those in the South Pacific. Eleven were discharged in 1945 and one in 1947. Their malarial attacks varied all the way from a dull headache with low grade of fever to hard shaking chills with temperature rising to 105 or above.

All of them took quinine dihydrochloride intravenously. We started off with 15 grains in 1000 cc. of glucose but usually finished up with 10 grains of quinine instead of 15 grains. Of the twelve cases two had two infusions, four had three infusions, two had five infusions and the other four had 6, 8, 10 and 24 infusions, respectively. All of them took other medication either at the time they were taking their infusions or after the acute attack had subsided. Atabrine, aralen, totaquine, quinidine and quinine were taken by some of the group with seemingly about the same effect. The acute exacerbation cleared up promptly and only in one case, the one with the 24 infusions, does a relapse keep recurring. He has had a total of five relapses altogether. Another has had four relapses and the rest of them have varied on down to no re-

TABLE 5

TIME PATIENTS STAYED WELL

Color & Sex	Less Than 3 Months	3-6 Months	6 Months 1 Year	1-2 Years	Total	No Report
White Male	11	9	14	20	54	3
White Female	19	47	48	46	160	6
Colored Male	3	4	3	2	12	6
Colored Female	7	3	1	10	21	2
Total	40	63	66	78	247	12

C M 9 Hematuria—Well 1 Year.

TABLE 6

TREATMENT TAKEN OTHER THAN QUININE INFUSIONS

Color & Sex	Quinine	Quinidine	Totaquine	Atabrine	Aralen	Total
White Male	3	7	14	3	1	28
White Female	9	45	64	11	5	134
Colored Male	0	2	3	0	0	5
Colored Female	2	4	3	0	0	9
Total	14	58	84	14	6	176

lapses at all. This group has responded similarly to the civilian except that some of the cases have been a little more difficult to cure. The relapses are not so severe as they were to start with and chills do not reappear in any of them. Headache, malaise and general bad feeling are the determining symptoms. Parasites have been found in all their bloods.

Good Results of Intravenous Quinine Therapy

(1) Complete relief from all symptoms in practically all patients.

(2) The drug is tolerated by all age groups, especially the aged.

(3) There is a general tonic effect to the whole muscular and nervous systems which might be partially due to the glucose.

(4) Many of the side effects of quinine by mouth are avoided by the intravenous route.

(5) There seems to be a definite decrease in its toxic effect.

Conclusions

(1) It is safe to use even in allergic individuals.

(2) It relieves the symptoms of chronic malaria.

(3) It may assist in completely relieving the patient of his infection.

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changes (periportal infiltration) so often observed in the livers of malaria-saturated Africans.

Many other questions remain to be answered. Firstly, what sequence of events determines a malarial relapse? Does the establishment of the blood infection terminate the exo-erythrocytic tissue phase or does this persist as a low-grade infection of the liver to ensure the persistence of the parasite? In a recent paper the same workers—Shortt, and Garnham—have partially answered these questions again in monkeys infected with *Plasmodium cynomolgi* which is analogous to the *P. vivax* of man. In another monkey which had in 3½ months been infected with thic organism a relapse was suspected and in its liver similar plasmodial masses were easily demonstrated. Thus evidence was obtained of the per-

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SPECIAL ARTICLE

Congestive Heart Failure

This summarization attempts to cover all of the known therapeutic information on the subject and is designed as a time-saving refresher for the busy practitioner.

Reprints available.*

Congestive heart failure, also known as myocardial insufficiency or cardiac decompensation, is a syndrome of broken compensation in which the heart is no longer able to perform the amount of work necessary for the body as a whole to continue on in its normal activity.[1] It usually occurs as a result of heart disease brought on by acute rheumatic fever, chronic rheumatic heart disease, arteriosclerosis, hypertension, coronary occlusion, hyperthyroidism or other conditions of this type. Functional disorders of the heart such as prolonged tachycardia and auricular flutter may also be responsible for bringing about this condition. However, no matter what the condition is which results in congestive heart failure the syndrome is made up of a series of symptoms which is due basically to the heart failing to maintain normal and adequate flow of blood to the organs and tissues. Venous stasis and the diminished blood flow result finally in tissue and organ anoxia.[2]

Symptoms

The earliest and most common symptom of congestive heart failure is dyspnea or shortness of breath, the degree of which is variable. The dyspnea is first noticed as the individual becomes conscious of a lack of adequate ventilation or an insufficient quantity of air. The respiratory rate is usually increased somewhat but not necessarily. Physical effort may bring on the dyspnea or it may occur spontaneously and rest may or may not cause it to subside immediately. Dyspnea is only of significance as a symptom of congestive heart failure if it occurs following an amount of exertion which ordinarily caused no distress, for excessive exertion in a normal individual may induce shortness of breath. Exertion following a heavy meal, climbing of stairs or a hill or walking against the wind usually is sufficient to induce dyspnea in the cardiac patient. It may be abrupt or gradual in onset. Disorders of rhythm such as auricular fibrillation are usually responsible for the abrupt onset. Dyspnea may pass rapidly into the more severe forms or it may exist to a minor degree for a long period before progressing but eventually it occurs even when the patient is resting.

The earliest symptoms and in some cases the only ones noted for a period of time are digestive disorders which include dyspepsia, fullness, bloating, belching and flatus. It is possible that the condition may be diagnosed erroneously as a disease of the liver, galbladder or digestive tract, particularly if there is also an epigastric or hypochondriac pain.

The patient may not always hold the heart responsible for all the symptoms but simply those which he feels in the area of the heart such as palpitation, fullness or pain in the precordial area, or pounding in the chest, neck or heart.[2]

Another sign commonly observed is that of increased venous pressure which may be missed because of failure to examine

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the patient for it. Examination of a patient suspected of having heart disease should include routinely an inspection of the veins on the backs of the hands or of the external jugular veins. Cyanosis, in some cases to marked degree, usually accompanies increased venous pressure. As the increased pressure progresses the pulsations visible in the jugular veins usually disappear. Jugular pulsation, however, may be practically constant in cases where the tricuspid valve is not functioning properly or is defective in its structure. Normal jugular pulsation is composed of 3 waves auricular, carotid and ventricular. In cases of deficiency in the tricuspid valve the predominant wave is ventricular and in some instances it may mask the other two. This type of venous pulse is known as the ventricular or systolic and can usually be observed in the hand veins. Frequently there is an expansile systolic pulsation in the liver.

A cough, which is usually troublesome and productive, is another common symptom. The sputum generally resembles the type observed in bronchitis. It may be blood-tinged or there may be spitting of blood, particularly where mitral stenosis is present. The sputum may appear brownish and contain phagocytes filled with blood pigment (heart failure cells) in cases where the left ventricle has failed for some time. Pulmonary congestion, which is frequently accompanied by transudation of serum into the alveoli, is usually responsible for the cough. Aortic stenosis usually makes it more troublesome. If the failure has advanced to a severe degree breathlessness when lying in a horizontal position (orthopnea) occurs. In severe cases this is present constantly.

Congestive heart failure is accompanied by another type of shortness of breath which occurs in attacks (paroxysmal dyspnea) and may or may not be preceded by dyspnea resulting from exertion. Such attacks may occur spontaneously or may be induced by the cough, a full bladder, abdominal distension, an orthopneic patient slipping off the pillow, bad dreams, or other minor disturbances. Paroxysmal dyspnea may occur only at night. Frequently it is described as cardiac asthma because of the wheezing respiration as well as sibilant and sonorous rhonchi in the lungs.[2] Aortitis, particularly syphilitic, hypertension or coronary scelerosis are usually responsible for paroxysmal dyspnea. Attacks of paroxysmal dyspnea eventually result in acute pulmonary edema which is in reality a more severe form of cardiac asthma beginning rapidly or abruptly. It is characterized by profuse transudation of fluid and red cells into the alveolar spaces. This results in expectoration of an abundant pink, frothy sputum.[2] Respiratory distress is extreme and many characteristics of shock and collapse may accompany a severe attack. Acute myocardial infarction may or may not be present. It is more common in congestive heart failure patients than in those with mitral stenosis. It provides evidence of acute left ventricular failure. Left ventricular failure may begin slowly over a period of years and the only signs of the condition may be discomfort in bed at night when not propped up on several pillows, a chronic annoying cough or effort angina to some degree, or a type of arrhythmia. Unfortunately the condition is not always diagnosed and the symptoms are treated singly whereas the patient would benefit from therapy of heart failure in these early stages.[1] In some cases insomnia may be the only symptom of left ventricular failure. It is not difficult to see how the real condition might be overlooked in such a case.[3]

The respiratory symptoms described are usually but not always accompanied by cyanosis of the lips and nail beds or of the more generalized type. There may be pronounced, moderate or slight weakness and ready fatigability. In some cases the patient may note palpitation, heaviness in the chest or a dull ache in the precardium.[2]

The respiratory distress is increased by pleural effusion which mechanically interferes with pulmonary ventilation. This commonly occurs and is usually less frequent on the left than on the right side. It may be bilateral. Diagnosis is based upon the common physical signs of fluid such as diminished chest expansion; impaired resonance, dullness or flatness on percus-

sion; impairment or absence of voice and breath sounds and tactile fremitus. If the lung is compressed by the fluid the transmitted voice may be bleating with an area of bronchial voice and breath sounds at the upper level. X-ray film or the fluoroscope will aid in diagnosis. The fluid may be withdrawn by means of a needle to establish diagnosis.

Venous stasis in the systemic circuit causes the development of dependent edema. Passage of fluid from the circulation into the tissues surrounding it is encouraged by the slower blood flow, the increased venous pressure and the usually augmented blood volume. The ability of the tissues to retain fluid is increased as a result of additional sodium retained there. Although such changes are not so important as is the impairment of circulation, failure to treat them properly will result in the establishment of a vicious circle. Symptoms of the development of such an edema include an unexplained gain in weight, and puffiness of feet or ankles toward night which generally disappears while sleeping because of the gravitational distribution of the edema. The dependent tissues of the body will be found to have this edema at all times if the quantity of fluid increases. The concentration of it in any tissue depends upon the position of the body.

As the edema progresses it finally is present all over the body (anasarca) and this condition is usually accompanied by pleural effusion and free fluid in the peritoneal cavity (ascites). Generalized edema may be marked and may develop either before or after the pleura and peritoneum are affected. Pericardial effusion may occur but is very difficult to determine.

Oliguria is frequently observed. Urinalysis reveals that the urine is concentrated with a specific gravity above 1.020; contains casts and albumin; and the urate content may be increased. It is necessary at this point to differentiate between a cardiorenal case and a congestive heart failure case. Congestion and venous stasis cause a deficiency in the renal function which in turn causes these changes in the urine. Digitalis and diuretic therapy will reverse these phenomena.

Prolonged hypertension and arteriosclerosis resulting in congestive heart failure may also cause nephrosclerosis due to the changes in the vessels. Examination of the blood reveals an increase in the nitrogenous metabolites, especially urea and nonprotein nitrogen. Congestive heart failure complicated by kidney disease results in retention of large quantities whereas in the uncomplicated condition the amount is small. Urinalysis to determine nephrosclerosis reveals certain irreversible phenomena such as a low and relatively stationary specific gravity and a large daily volume.

Examination reveals that the liver is congested and enlarged. The patient usually has a feeling of weight or fullness in the upper abdomen. In those cases where the liver has enlarged rapidly there will also be pain and tenderness. Expansile pulsation usually accompanies any functional or organic insufficiency of the tricuspid. Chronic liver congestion is not accompanied by tenderness and pain whereas in cases where the capsule is rapidly stretched they are present. Jaundice of a slight or moderate degree commonly occurs but usually in the later stages, making the prognosis unfavorable.

The patient with congestive heart failure may have a history of some other heart condition such as angina pectoris or acute myocardial infarction. However, symptoms of these conditions may be obscured after congestive heart failure has begun its course but can be observed if sought. Auricular fibrillation is responsible for bringing on congestive heart failure and the patient may not be cognizant of the irregularity which has developed.

Primary right ventricular failure is usually associated with mitral or congenital heart disease or with an obstruction of some nature. Symptoms of this condition include dependent edema; enlarged and congested liver; signs of engorgement of other abdominal organs; and secondary congestive respiratory signs. In those cases where right ventricular failure develops at an early stage such as in rheumatic lesions of the tricuspid valve anasarca frequently appears

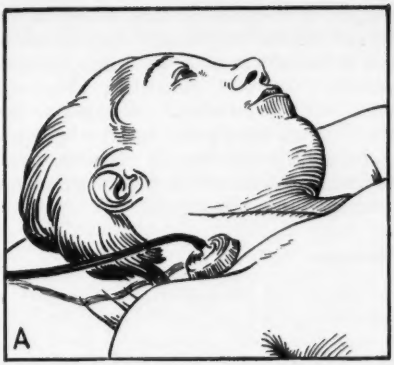

Fig. 1. A. Method of recording the venous pulse. The suction cup is applied over the jugular bulb on the right side of the neck.

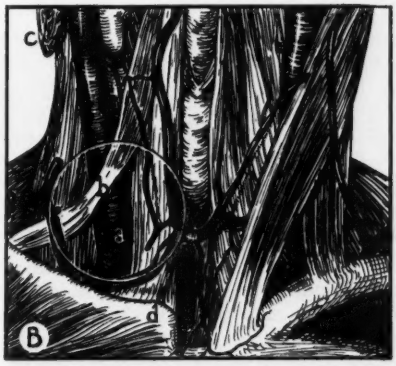

Fig. 1. B. Anatomical position of the jugular bulb. a. Jugular bulb; b. Omohyoid muscle; c. Cut edge of the sternocleidomastoid muscle; d. Clavicle.

earlier and continues for several months or years. The prognosis in right ventricular failure is more favorable than in left ventricular failure because the right ventricle can recompensate more quickly and frequently than can the left ventricle despite the fact that the right decompensates more easily.[1]

Clinical Course

The clinical course of congestive heart failure varies considerably. Usually the patient has successive attacks of failure each one growing more severe and more prolonged and the intervals between shortened considerably. As the attacks progress therapy becomes less adequate until finally it is of no value and the patient dies. In other cases the patient responds to therapy to the same degree through several attacks but suddenly shows the symptoms of exhaustion, frequently acompanied by cachexia, and rapidly declines until death ensues. When congestive heart failure develops as a result of an infection or because of multiple pulmonary thromboses (common in cases of mitral stenosis) the symptoms develop quickly and death may occur within a few days or weeks. In some cases the edema of the lungs is so acute as to cause death in a few hours. Other conditions which may hasten death include lobular pneumonia, mesenteric thrombosis or an embolism to the lungs or brain. Aortic lesions of the heart may cause death without the development of congestive heart failure. Younger patients having an inactive heart disease may experience attacks of failure at long intervals early in the disease and it may be several years before the disease shows progress.

Several tests have been devised to enable the physician to test the functional efficiency of the heart but no one test gives complete information so that it is necessary to run several kinds and study the coordinated data. Of the group the tests which are of greatest value include[2]: (a) Measurement of the vital capacity of the lungs by means of a spirometer. Because stasis and congestion, brought about by left ventricular failure or mitral stenosis, reduce this capacity it serves as an indicator. The average maximal volume of air expired in a single inhalation for men is 2.61 liters per square meter of body surface and for women, 2.07 liters per square meter (normal variation does not exceed 15 per cent).[4] (b) Estimation of venous pressure by elevating the head and torso to the level at which the external jugular vein (right preferred) collapses. The level of pressure is taken as the height of the vein above the

right auricle which normally ranges from 7 to 10 cm. (c) Venous pressure may also be measured by determining the height necessary to raise the hand above the auricle in order to collapse the distended veins. (d) A water manometer connected to a palette may also be employed to measure venous pressure. The patient's hand is supported at the level of the right auricle and a distended vein on the back of the hand is collapsed by means of the column. The height of the column at this point is the reading taken. (e) Venous pressure is most accurately measured by a method developed by Moritz and von Tabera who inserted a large needle into one of the antecubital veins. By connecting the needle to a manometer the height of a column of saline or the blood can be measured. The normal range of 7 to 10 cm. is usually doubled or trebled in severe cases. (f) Velocity of blood flow or circulation time is another indicator of the heart efficiency. A harmless substance is rapidly injected into a specified vein and its time of arrival at certain points of the body determined. An arm to lung time of 4 to 8 seconds is the average when 0.6 cc. of equal parts of ether and normal saline are injected intravenously. Detection of ether in the patient's expired air is the endpoint. Arm to tongue time normally ranges from 10 to 16 seconds as determined by the development of a bitter taste when 5 cc. of a 20 per cent solution of sodium dehydrocholate is administered or a sweet taste when saccharin is given. A complicated technic more suitable for research than for clinical use is the injection of radium C into an arm vein and using a special detector apparatus to determine the time it arrives at various points of the body. The averages found with this method are: 7 seconds for arm to heart, 18 seconds for arm to arm and 11 seconds for pulmonary circulation.[5] In cases of congestive heart failure these times are longer than normal but tend to become normal as the patient recovers. Various other methods also have been developed.[6] (g) Cardiac or systolic output of the heart or minute volume may be measured by an acetylene method which is more applicable to research use than to clinical use because of its complexity.[7] (h) Injection and measurement of a dye is employed to determine the total circulating blood volume, which is commonly increased in congestive heart failure and decreased when it is brought under control. Because blood volume is influenced by many factors this method is not too reliable.[8]

Therapy

Therapy in congestive heart failure is directed toward improvement in the function of the heart, reduction of the burden of the heart and removal of the edema. It is almost impossible to restore the heart to normal anatomically and to eliminate the etiologic disease which brought about the changes. There have been some exceptions to this as for example: surgical obliteration of patent ductus arteriosus, excision of coarctation of the aorta, decortication of constrictive pericarditis, removal of burden of thyrotoxicosis, replacement therapy in vitamin or endocrine deficiencies, eradication of active infection in conditions such as subacute bacterial endocarditis and in some cases of cardiovascular syphilis.

Rest

Physical and mental rest are important in the therapy of congestive heart failure because it is necessary that the amount of work required of the heart be decreased in order to restore cardiac reserve. Bed rest is considered essential but the kind and duration depend upon the severity of the condition. It is far wiser to institute too strict a routine than too lenient a one. There are several schools of thought concerning bed rest. Some[9] believe that in severe cases absolute bed rest with no active movement is indicated. The patient should be fed and lifted or moved by someone else when a change in position is desired. It is essential that the bedpan and urinal be used except in those instances where discomfort and straining are too great. It may be better for the patient to use a commode near the bed or to go to a nearby bathroom at times. The patient may be allowed to seek the most comfortable position in bed. Most

patients feel better in a semi-sitting position which allows for an increase in vital capacity and minimizes any respiratory distress. There is available a special type of bed which raises the head and lowers the extremities (orthopneic position). If this is not available the patient's shoulders and head may be elevated by means of pillows or a backrest. The tendency to slip down in bed is hindered by placing a rolled pillow or blanket under the knees. Another means of raising the head and shoulders is by placing 9 inch high blocks under the head of the bed.[9] When the patient has improved sufficiently to get out of bed it should be done very gradually and cautiously. The first day he may hang his feet over the side of the bed until he is fatigued. If no untoward reactions, such as dyspnea or rise in pulse rate, occur, he may be assisted to a chair near the bed on the following day, remaining there until fatigue occurs. The next day he may get into the chair twice and on the next day he is allowed a few steps. If no untoward reactions occur his activity is increased each day and within a week or ten days he may be able to move about alone.[9]

Another authority[10] states that bed rest should not be absolute unless the heart failure is associated with myocardial infarction or a severe infectious state and should be discontinued as soon as possible. A moderate degree of movement such as foot exercises, change of body position and self-feeding should be allowed. By weighing the patient daily his status can be followed closely and he also gets a form of mild exercise. Bathroom privileges are allowed if preferable and particularly if straining is necessary when the bed-pan is used. Absolute bed rest is considered dangerous because of the possibility of development of pulmonary complications such as hypostatic pneumonia and infarction; reduction of peripheral blood flow with a resultant venous thrombosis and subsequent pulmonary embolism and infarction; development of osteoporosis and muscular atrophy; vasomotor instability; the formation of renal calculi and obstructive uropathy; development of chronic constipation with cathartic habituation; formation of decubitus ulcers; and collapse and sudden death following exertion in using bed pan.[10] Placing the patient in bed may cause some of the fluid in the extremities where it is less harmful to shift into the lungs and cause congestion before drug therapy to move it to the kidneys can be accomplished.[10, 11] Absolute rest also leads to psychic invalidism often accompanied by cardiac neurosis of varying degrees.[10]

Some physicians allow the patient to get out of bed for several hours each day as soon as there is no longer severe dyspnea at rest[12]; others encourage early ambulation and sitting up to eat but advise the patient to lie as flat as is possible for him to do comfortably for as much of the day as he can.[13] It has been stated that the erect posture when maintained for long periods of time even in normal persons predisposes to salt retention and in heart patients may lead to nocturnal dyspnea. Sitting or standing for short periods is not believed to stimulate the salt-retaining mechanism and so it is advised that short periods of time be spent in a chair early in recovery. This is believed to improve the physical condition, minimize the risk of phlebothrombosis and not to retard diuresis or recovery.[13] One authority has stated that rest in bed encourages diuresis.[14]

Mental rest is extremely important to the cardiac patient for excitement increases the work of the heart. Anxiety states should be avoided.[10] The number of visitors should be restricted and those allowed should be careful not to excite the patient by their conversation or prolonged stay. In severe congestive failure any reading material or radio programs which might cause excitement should be prohibited. When the patient shows minimal or no signs of cardiac failure he should be given advice on the proper adjustment to his disease and his problems of livelihood. Occupational therapy is of value in restoring his confidence as a useful member of society.[9] A rehabilitation program should be instituted with the help of some social service agency. It is necessary to secure cooperation of employers who are doing the type of work and

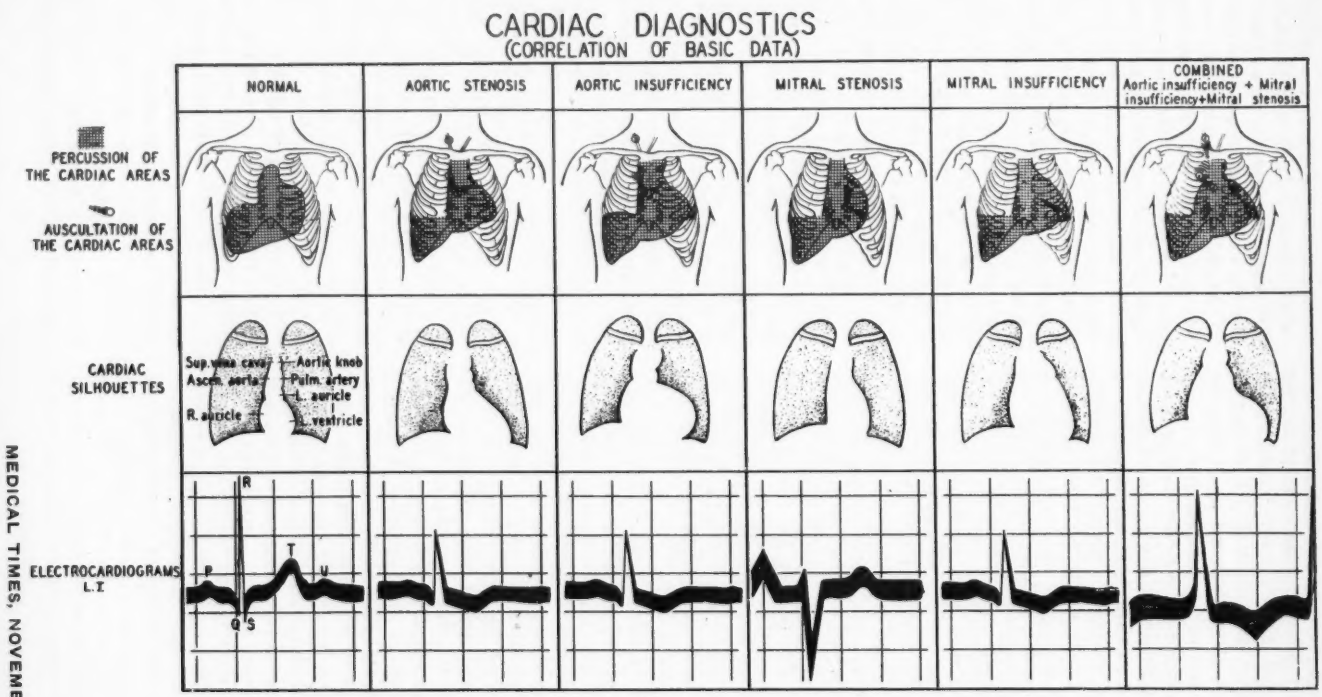
CARDIAC DIAGNOSTICS
(CORRELATION OF BASIC DATA)
NORMAL
AORTIC STENOSIS
AORTIC INSUFFICIENCY
MITRAL STENOSIS
MITRAL INSUFFICIENCY
COMBINED
Aortic insufficiency + Mitral insufficiency+Mitral stenosis
PERCUSSION OF THE CARDIAC AREAS
AUSCULTATION OF THE CARDIAC AREAS
CARDIAC SILHOUETTES
Sup. vena cava
Ascen. aorta
R. auricle
Aortic knob
Pulm. artery
L. auricle
L. ventricle
ELECTROCARDIOGRAMS L.I
R
P
T
U
Q
S

Figure 2.

maintaining the hours of employment fitting the patient.[10]

Complete recovery is necessary before the patient can be permitted undue exertion or coitus. The patient should be advised without causing undue anxiety to watch for any signs that the condition might be recurring, for disappearance of symptoms of cardiac failure is no guarantee against recurrence.

A recent study has shown that a cool and comfortable atmosphere is important in congestive heart failure because it eliminates excitation of the thermo-regulatory mechanism which involves in turn considerable work for the cardiovascular system.[15]

Some of the burden on the heart and distress of the patient may be eased by the use of oxygen given by means of nasal catheter, face mask or tent.[2]

Some state that rest in bed is essential only for patients with actual congestive heart failure and that patients with organic heart disease who do not have the former may be ambulatory.[9] It is also believed that the degree of physical activity allowable for ambulatory patients depends upon the degree of cardiac reserve as well.

When the congestive heart failure patient has convalesced and becomes ambulatory he should be advised as to his activities and occupation. A sedentary occupation with reasonable hours is preferable. Exercise is permitted in moderation but all highly competitive sports should be avoided. If exercise as prescribed brings on any signs of distress to the heart it should be discontinued. The patient should not indulge in any such exercise on very hot or rainy days. Hot baths, steam baths and sweat cabinets should be avoided. Coitus should not be undertaken for several months after an attack. If the patient smokes or indulges in alcoholic beverages he should do so in moderation. Rest periods should be advised.[9, 10] One authority recommends rest in the middle of the day and before the evening meal in order to cause a redistribution of the blood and a maximal basal cardiac output. This is not so likely to occur with patients who are up all day.[13] In patients with fairly well compensated heart lesions one flight of stairs is permitted but patients who are not well recovered should be advised to live on a ground floor. Localities with altitudes over 1500 feet should be avoided.

In the over all picture of rest and activity it is necessary that the degree be adjusted to the individual patient's condition at all times.

Diet

Diet in congestive heart failure is also a matter of controversy. Some recommend very strict restrictions whereas others believe that it should be well balanced but not too large an amount of food consumed. It should not contain foods which will cause gaseous distention. In the presence of edema the salt intake should be reduced to approximately 3 Gm. daily. Spicy foods and condiments should be avoided. If the diet is reduced in respect to salt intake the total fluid intake for 24 hours need not be restricted. In some cases where the salt intake is reduced as low as possible, fluids may be forced to a moderate degree.[16-18] The acid-ash, salt-poor diet which has been used successfully by several workers is constructed on the basis that sodium, especially sodium chloride, is much limited; that meat, chicken, fish, eggs, corn and wheat products yield an excess acid ash; and that milk, vegetables and fruits with the exception of prunes, plums and cranberries yield an excess alkaline ash. Unfortunately such a diet is tiresome and has a flat taste. For this reason there have been developed certain salt substitutes which have been made available. They contain compounds which flavor the food without harming the patient.

In studies on the restriction of fluids it has been found that restriction of fluids might lead to dehydration with disorientation so that in most cases the fluid intake is not restricted and in some it is forced.[19] One group recommends an unrestricted diet for patients who remain compensated with digitalis preparations. They also feel that the restriction of salt intake is more important than fluid intake. In patients who have decompensation in spite of digitalization and who require an occasional mercurial diuretic the salt intake should be restricted to 3 to 4 Gm. daily, which means

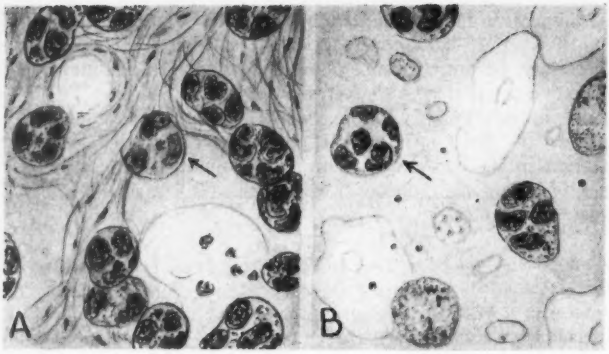

Fig. 3. Heart failure cells. These are phagocytes or tissue cells containing hemosiderin. They have a Berlin Blue reaction.
a. In the lung.
b. In unstained sputum.

that an average diet can be prescribed but no salt should be added in cooking. For those patients having advanced myocardial failure uncontrolled by the usual measures the daily salt intake should be restricted to 1.5 to 2.0 Gm. With this restriction the edema can be controlled and possibly eliminated entirely and the need for frequent use of mercurial diuretics is reduced. If the latter are absolutely indispensable the salt intake should not be too rigid so that diuresis is adequate and symptoms of salt deprivation do not follow diuresis. Greater fluid intake is permitted so that the annoying thirst is avoided. In obese patients or those in bed because of edema a low caloric diet is indicated to decrease metabolism and oxygen demands. For patients with superimposed nutritional edema and those losing large quanities of protein in the urine or by frequent paracentesis a high protein diet is advised.[10] One author found that there were slightly subnormal albumin levels with slight compensatory increases in globulin values in the plasma proteins of patients with edema due to congestive heart failure. After the edema had cleared the blood proteins did not rise to normal levels immediately, possibly due to liver dysfunction. He therefore recommended a high protein and acid-ash, low-salt diet.[20] Another author recently confirmed the finding that plasma protein deficit frequently but not uniformly occurs in congestive heart patients and therefore recommends high protein diets unless there are other contraindications.[20a]

In those cases where the edema is very severe or has progressed to anasarca the Karell diet may be of use. The very restricted Karell diet is made up of 200 cc. of milk 4 times daily.

Administration of glucose, thiamine hydrochloride and ascorbic acid is frequently of value for the support of the cardiac musculature. The heart is dependent upon carbohydrate as a source of energy in order for it to function properly.

Laxatives

In order to prevent any exertion on the patient's part such as straining at stool it may be necessary to give a mild laxative such as mineral oil, cascara, milk of magnesia or a combination of several. A small enema or a glycerin suppository may be useful.

Sedatives and Hypnotics

Sedatives or hypnotics may be of value in congestive heart failure cases to relieve a troublesome cough, dyspnea or orthopnea for it has been found that sleep and rest even though obtained by means of drugs are beneficial. Codeine in doses of 15 to 60 mg. may be given but usually morphine will be necessary. It is given in doses of 10 to 20 mg. subcutaneously. If Cheyne-Stokes respiration is present a smaller dose should be used. Other compounds closely related to morphine may be used if preferred. The hypnotics such as morphine and its related compounds cannot be given longer than every night for 1 week with-

out danger of addiction. As soon as possible they should be replaced by other sedatives suitable for the purpose of keeping the patient quiet, calm and free from anxiety during the day or for the purpose of producing sleep. The barbiturates are indicated to supplant the course of morphine and also to quiet the patient during the day. Phenobarbital is usually given in doses of 0.015 to 0.032 Gm. 3 times a day and the dosage increased to 0.1 Gm. half an hour before time for sleep. Other barbiturates also may be used satisfactorily. In administering the barbiturates or bromides to older patients, especially those having cerebral arteriosclerosis, it is necessary to observe the patient closely in case he should develop mental disturbances such as restlessness, disorientation or delirium. Chloral hydrate in doses of 0.2 to 0.5 Gm. 2 to 4 times a day is useful in the patient with hypertension. At bedtime 1.5 Gm. should be given to induce sleep. Chloral hydrate may also be used with an equal quantity of a bromide. Some object to chloral hydrate because of its bad taste and no superiority over barbiturates or bromides. Paraldehyde is used in doses of 4 to 16 cc. and produces sleep promptly without a depression of the respiration or circulation. It may be administered orally in the form of an elixir containing 25 per cent of the drug or alone on shaved ice or in whiskey. Rectally the dose is the same and it is administered in an oil enema or in 120 to 200 cc. of warm tap water. Intramuscularly the dose is 4 to 8 cc. Some object to this drug because of the unpleasant odor it leaves on the patient.[2, 9]

Digitalis Preparations

Digitalis or one of its preparations is indicated in congestive heart failure regardless of the type of underlying heart disease, precipitating factors, age of patient, type of rhythm, heart rate or presence of heart block. It is not indicated in the following conditions if congestive heart failure is absent: acute infections with toxemias such as pneumonia; myocardial infarction; tachycardia; peripheral shock; not for routine administration preoperatively.[10] The only true contraindication for digitalis is toxicity. It is necessary to be familiar with the signs of toxicity for this reason. They include headache, nausea, vomiting, diarrhea, colored vision, ectopic beats, auriculoventricular block and changes in the electrocardiogram showing depression of the S-T segment and lowering or inversion of the T waves.[2]

Pharmacologically digitalis acts by increasing the force of systolic contraction, which results in an increased mechanical efficiency of the heart muscle to convert more of its energy into external work whereas the undigitalized muscle is limited.[2] The former also can do a fixed amount of work and expend less energy doing it. Digitalis, however, by its vagal or muscular action, may also affect all portions of the heart dependent upon their inherent functions of rhythmicity, conductivity, irritability and contractility and alteration of these by pathological processes. Thus a multitude of actions is usually observed in every patient with any one function usually dominating the response clinically. Initial or small doses of digitalis will cause a vagal action which is secondary to reflex changes resulting from improved cardiac dynamics or stimulation of nerve centers. A muscular action is effected on the auricular muscle by larger doses. These vagal and muscular actions in the conduction and refractory period oppose each other in effect. Increased myocardial efficiency is primary and slowing of the heart rate is secondary to it. Earlier reports believed that this slowing of the heart rate was responsible for the observed improvement of cardiac compensation but this may be noted before there is any appreciable slowing of the heart rate. In patients with normal sinus rhythm, compensation is restored without any significant change in the heart rate. In auricular fibrillation patients given digitalis and atropine simultaneously, the compensation occurs in the usual time as a result of the direct action of the drug upon the heart. The slowed ventricular rate is not affected until this muscle action is dominant. In very rare cases of auricular fibrillation compensation may be restored completely without any alteration of tachycardia. Bed rest alone for patients with

fibrillation has been shown to restore compensation, which is followed by a slowing of the ventricular rate just as in patients with normal sinus rhythm. Digitalis will not slow a rapid auricular fibrillation in the absence of myocardial failure unless the larger toxic doses are employed.[10]

It is important to remember not to treat the heart rate but the patient, emphasizing the attainment of a maximum myocardial efficiency without regard to heart rate. A rough index of digitalis action is the slowing of the heart rate, especially in auricular fibrillation patients. Digitalis therapy should not be stopped because the heart rate is slowed unless there are signs of toxicity present.[2, 10]

Cumulative Action

Digitalis has a cumulative action which may result in toxicity. However, this depends upon the size of the dose, the latency of action, the time interval between doses and the rapidity of dissipation. The cumulative process is self-limiting, as shown by the fact that continuous daily therapy may be carried on for 8 to 12 weeks before any single dose level attains its maximum cumulative effects. No greater effect will then be achieved by this dosage level.[10]

Latency of Action

Latency of action of cardiac glycosides is not significant when they are given orally because of their variation in absorption and dissipation but it is of significance in intravenous administration. At this point it should be explained that the glycosides are the active constituent found in all digitalis or similar preparations. They will be discussed in detail later. Ouabain or g-strophanthin, strophoside and K-strophanthin are all rapid in onset of action; digoxin, lanatoside C and gitalin are moderately rapid; and digitoxin, digitalis purpurea, digitalis lanata, purified extracts of digitalis containing large amounts of digitoxin and squill are all slow. The rate of dissipation follows much the same order so that ouabain effects disappear most rapidly and digitoxin effects last the longest. Completeness of absorption cannot be ascertained due to the lack of satisfactory methods. It is necessary to consider in this respect the latency of action, dissipation, and similarity of effects noted with wide dosage range. The glycosides vary in their degrees of effect inherently so that certain differences may not be due to absorption variances. The glycosides commonly used are absorbed sufficiently uniformly in adequate amounts so as to provide satisfactory digitalization and maintenance.

Products

Digitalis purpurea and related plants are mixtures of several glycosides and inert materials. Consequently standardization has always been a problem. The official U.S.P. bio-assay is performed with cats and establishes the digitalis unit as that quantity of digitalis as compared to the U.S.P. XIII reference standard powder of digitalis leaf which is required to produce, when administered intravenously in the form of a specially prepared tincture, cessation of the heart beat in a group of test cats. It represents the potency of 0.1 Gm. of the U.S.P. digitalis reference standard.

To overcome the variability of the different digitalis preparations a human assay has been developed. Studies have shown that there is considerable difference in the effects produced by various digitalis products and also by the various purified glycosides. Some tablets have been found to produce 5 times the effect as another and in the case of the purified glycosides one tablet may produce ten times as much effect as another. By means of the human assay it has been shown that digitoxin is practically completely absorbed (its oral and intravenous doses are the same) whereas only about 20 per cent of a dose of digitalis is absorbed and only about 10 per cent of a dose of lanatoside C.[10a-d]

There are available commercially a myriad of digitalis and digitalis-like preparations. Official in the U.S.P. XIII is Digitalis purpurea (Digitalis leaf) which consists of the dried leaf of *Digitalis purpurea* Linné and contains a mixture of cardiac glycosides, chiefly digitoxin, gitalin and gitoxin.

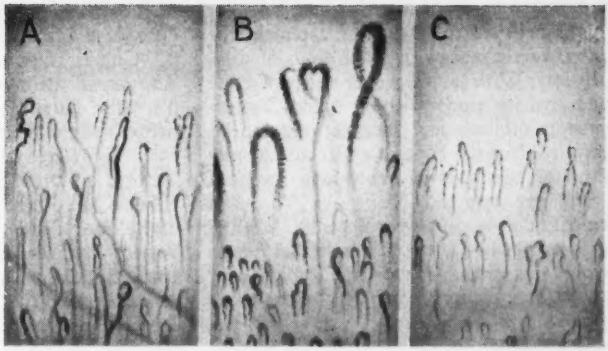

Fig. 4. Capillaries of the skin over the nail.
A. Normal.
B. Insufficiency with congestion of the superficial vessels.
C. Insufficiency with contraction of superficial vessels.

Numerous firms make this available in tablets, ampules, tinctures and fluidextracts. Digitalis purpurea extract is marketed by a number of companies under various tradenames in the form of tablets, capsules, ampules and tinctures in varying potencies based on the official unit. Some of these are prepared fat-free, others are alcoholic extracts, nonalcoholic extracts and aqueous preparations. Digitalis lanata, the dried leaf of *Digitalis lanata* Ehrlich, contains a mixture of glycosides known as lanatosides A, B and C. It is standardized according to the official unit and marketed in tablet form. Digoxin U.S.P. is a crystalline glycoside obtained from *Digitalis lanata* Ehrlich and is available in tablets of 0.25 mg. and in ampules containing 0.5 mg. in an alcoholic solution (7 per cent). Digitoxin U.S.P. is the pure crystalline digitoxin or a mixture obtained from *Digitalis purpurea* Linné, consisting chiefly of digitoxin. This product is available in the following dosage forms: tablets, 0.1 mg. and 0.2 mg.; capsule in oil, 0.1 mg. and 0.2 mg.; ampule, 1 cc. containing 0.2 mg. and 2 cc. containing 0.4 mg. Various firms have this available. Lanatoside C, U.S.P. is the crystalline glycoside obtained from *Digitalis lanata* Ehr. and is available in 0.5 mg. tablets and ampules of 2 cc. A mixture of crystalline glycosides, lanatosides A, B and C, in the approximate ratio of 47:16:37, is marketed in tablet, tincture, suppository and ampule form. Crystalline ouabain or G. strophanthin is marketed in ampules of ½ cc. equivalent to 0.1 mg. and 2 cc. to 0.5 mg. Strophanthin is a mixture of glycosides obtained from Strophanthin Kombé and assayed against the U.S.P. ouabain reference standard. It is available in ampules of 1 cc. containing 0.34 mg. or 0.65 mg. and tablets of 0.13 mg. and 0.65 mg. K strophoside is a glycoside obtained from Strophanthus Kombé which is available in ampules of 0.5 cc. containing 0.25 mg. and 1.0 cc. containing 0.5 mg. Gitalin is an amorphous glycoside derived from *Digitalis purpurea* Linné and is available in 0.75 mg. tablets. There are several preparations of squill available as follows: (a) the water insoluble glycosides of *Urginea indica* marketed in plain or coated tablets of 1.0 mg.; (b) mixture of 2 parts crystalline scillaren A and 1 part amorphous scillaren B extracted from *Urginea maritima* and marketed in tablets of 0.8 mg.; tincture of which each cc. contains 0.8 mg. and a suppository containing 1.0 mg. and ethyl aminobenzoate: (c) amorphous scillaren B extracted from *Urginea maritima* and available in ampules of 1 cc. and containing 0.5 mg.

In the selection of the product to be given it is necessary to consider various factors. The glycosides possess certain advantages over the whole products as follows: (a) potency is constant; (b) a rapid or prolonged dissipating glycoside may be chosen according to the need; (c) absorption is uniform. Some have claimed that the glycosides cause less local gastro-intestinal

irritation such as nausea and vomiting but this is believed to be an overstatement for this is rarely seen with usual doses of digitalis leaf. With toxic doses of either of these true toxicity signs will be noted. Unfortunately digitalis leaf powder preparations vary in glycoside content and consequently although they may be equivalent in official units they may vary clinically. The wise practitioner is one who becomes familiar with one or two preparations so that he can avoid this possible variation which may result from using products from numerous companies.[21]

One author in summarizing the known information recommends the following procedure for the use of digitalis:[1] (a) Use digitoxin as the routine digitalizing drug; (b) use digitalis leaf as a second drug in cases where economic considerations are a factor because the latter is less expensive and in those cases where switching products is psychologically advisable; (c) have ouabain available for emergency intravenous injection; and (d) in unavoidable intramuscular administration use one of the glycosidal mixtures.

Administration

The basic principle of digitalization is the administration of a digitalis preparation until the therapeutic effect is accomplished or until toxicity develops. There are several different methods which are employed: (a) The slow method involves a dose of 0.1 Gm. of the powder or 1 cc. of the tincture 3 times daily, which results in digitalization of the average patient in approximately 7 to 14 days.[22]. This method is particularly valuable in treating ambulatory patients, patients who must be digitalized with care or patients who do not require rapid digitalization. The basis for this method is the administration of single daily doses larger than the estimated maintenance doses, resulting in slow digitalization. (b) An even slower and more conservative method is that which involves giving approximately two-thirds of the calculated dose in 24 hours. One-half of this calculated dose is given at once to the patient, followed by one-quarter of the calculated dose 6 hours later and one-sixth of the dose 6 hours following the previous dose. If digitalization is then not complete 0.1 Gm. is given every 6 hours until it is. The usual maintenance dose necessary is 0.1 Gm. daily. Because a majority of patients with a severe failure may not be fully digitalized this method is not satisfactory. To attain a therapeutic effect most patients need additional medication. Full digitalization may not always be attained despite the beginning of therapeutic effects. Because a large dose is necessary it may border on the toxic side and may cause local gastro-intestinal irritations. (c) The rapid or multiple dose method developed by Eggleston and considered by some to be the most suitable[10] is based on the principle of administering the largest, safest dose initially followed by increments at definite intervals. The patient is given 0.15 Gm. of the powder or 1.5 cc. of the tincture (each cc. considered the equivalent of 1 cat unit) per 10 lbs. of body weight in the first 24 hours. It is given in divided doses of one-half the calculated dose at once, one-quarter 6 hours later, one-eighth 6 hours after the second dose and one-sixteenth of the calculated dose twice at 6 hour intervals.[22] With this method digitalization is usually completed in 24 hours. It is believed by some that[10] the desired therapeutic effect is obtained with greater safety whereas others[22] state that the average patient cannot tolerate the high dosages and shows symptoms of toxicity when three-quarters of the dose has been given. It is recommended that such a course be given while the patient is hospitalized. The patient should have had no digitalis, its glycosides or related compounds for at least 3 weeks prior to this and electrocardiographic studies should have been made.[22] In Table I are shown the dosages for the various preparations according to this method. (d) Intravenous or parenteral administration of one of the digitalis glycosides or related compounds results in very rapid digitalization but should be employed only in emergencies. Patients who are unable to take oral medication or who are in extremis should be given a course of initial digitalization by this method. Because the water-soluble glycosides are not so well absorbed

Table I

PREPARATION	INITIAL DOSE	DOSE EVERY SIX HOURS
Digitalis leaf or purified extract	0.4-0.8 Gm.	0.2-0.4 Gm.
Digitoxin	0.4-0.8 mg.	0.2-0.4 mg.
Digoxin	1.0-1.5 mg.	0.5-0.75 mg.
Lanatoside C	1.5-3.0 mg.	0.75-1.5 mg.
Lanatosides A, B and C comb.	1.32-2.64 mg.	0.66-1.32 mg.
Squill (Urginea Maritima)	2.0-4.0 mg.	1.0-2.0 mg.
Squill (Urginea Indica)	3.0-6.0 mg.	1.5-3.0 mg.
Gitalin	2.0-4.0 mg.	1.0-2.0 mg.

from the subcutaneous tissues and are irritating as well, the method of choice is intravenous injection.[2] This method should not be employed in patients who are already digitalized or who have taken a digitalis preparation within a period of at least 2 weeks. Patients with auricular fibrillation respond better to this mode of administration than to the others. The total dosage may be determined by the slowing of the ventricular rate. Following the establishment of digitalization, oral preparations should be given for maintenance. The product chosen for this purpose should be rapidly acting and rapidly dissipating to avoid any continuance of toxicity if it should develop. One of the purified glycosides is usually employed. Ouabain is used considerably for this purpose. One dosage schedule employs a dosage of 0.25 mg. every 1 to 2 hours or longer until a total dose of 1.0 mg. has been attained. In extreme cases the initial dose may be 0.5 mg.[2] It is recommended that the dose be placed in 10 cc. of liquid and injected over a period of 5 to 10 minutes.[23] Another group recommends an initial dose of 0.5 mg. provided, as stated before, that the patient has had no digitalis or related compounds for at least two weeks.[10, 24] It is stated that most conservative practitioners give only one dose and if necessary do not give another for at least 24 hours.[1] In those cases where auricular fibrillation is marked and therapeutic effect can be easily observed doses of 0.1 mg. may be given at half-hour intervals following the initial dose.[10,24] The chief object of this therapy is to keep the patient alive and restore him to a status where oral medication can be given. Digitoxin, in a dosage of 1.0 to 1.25 mg. for complete digitalization, may be used if injected slowly. It has greater persistence of action (2 to 5 days) than has ouabain (eliminated almost totally in approximately 24 hours).[2] Some believe that strophanthin is more useful.[9] It is given in an initial dose of 0.25 to 0.50 mg. diluted in 10 cc. of dextrose solution and injected slowly. A second dose of 0.25 mg. may be given 6 hours later. Total dosage in 24 hours should not exceed 0.75 mg. Maintenance doses of 0.25 to 0.50 mg. (rarely) may be given but oral medication should be used as soon as possible (0.1 Gm. of digitalis may be administered orally immediately after the last injection). Table II shows the dosage of the various preparations which may be used for this purpose. (e) Combined oral and parenteral administration initiates digitalization with a safe dose of a rapidly acting, rapidly dissipating glycoside which supplements and maintains the therapeutic effects brought about by an oral product given simultaneously. This method is of especial value in emergency pre-operative and obstetrical cases but it is also of value in every type of heart disease without regard to the underlying rhythm. The rapid action of a parenteral product is combined with the safety of the comparatively slow oral product. It requires approximately 6 to 12 hours to develop complete digitalization. This method eliminates the need for giving any further digitalis therapy at certain intervals, thus eliminating the calculations required in the other methods. A maintenance dose is begun 24 hours after establishment of digitalization. Toxic symptoms rarely develop and are minimal when they do. The dosage schedule for this method is a single dose of any rapidly acting glycoside given parenterally simultaneously with a single dose of any digitalis preparation given orally.[10] One such plan gives 0.5 mg. of ouabain intravenously and 0.6 Gm. of digitalis leaf orally. The oral dosage is modified to 0.4 Gm. for patients under 125 lbs.; 0.6 Gm. for 125 to 175 lbs.; and 0.8 Gm. for over 175 lbs. A maintenance dose is established by trial.[25] The dosages should

be decreased in cases where the patient has had a recent myocardial infarction. This method also should not be used with patients who have had any digitalis preparation within the past 2 weeks. (f) Rectal administration of digitalis and its related preparations is recommended for those patients who cannot tolerate the drugs orally or for unconscious patients who do not need rapid digitalization. Splanchnic congestion may cause frequent vomiting, thus eliminating the possibility of giving oral medication. In order to allow for absorption the oral dose should be increased by 25 per cent. The drug may be given in a suppository containing the powdered leaf or in a retention enema consisting of one of the liquid preparations in a small quantity of warm water. A small cleansing enema should precede this type of therapy. If the nausea and vomiting, which prohibit oral medication, are due to the congestive heart failure, one or two large rectal doses will be sufficient to control the condition and allow for oral medication.

Administration of digitalis to patients with auricular fibrillation should slow the ventricular rate to 70—90 per minute. If the heart rate is then increased as a result of exercise it can be assumed that the slowing is of vagal origin and it is necessary to administer more digitalis to bring about extravagal slowing so as to give the heart greater protection. Frequently the risk of toxicity must be run because therapeutic effects are achieved at this level only. Following initial digitalization most patients require further therapy in order to maintain the compensation achieved and to prevent recurrence of decompensation. It is not calculated on the basis of the amount of digitalis dissipated or excreted each day. The maintenance dose for digitalis leaf varies from 0.1 to 0.3 Gm. daily and for digitoxin from 0.1 to 0.2 mg. It is necessary of course to adjust this dosage to the needs of the patient. A very rough guide for establishing the maintenance dose is the heart rate but it is not recommended. Poor maintenance may occur if therapy is discontinued when the heart rate is 60 per minute or below and no toxic symptoms are observed. The heart muscle has a peak of efficiency at a certain optimum rate in each individual. The heart rate will adjust itself to the basic demands after adequate digitalis therapy has established maximum efficiency of contraction. A slow rate makes a large heart more efficient. Inadequate maintenance as well as inconvenience to the patient may result if the maintenance dose is divided. This is especially true of rapidly dissipating cardiac glycosides. Therefore it should be given in one dose and preferably in the morning. The maintenance dose depends upon several factors and may have to be changed as they vary. Patients with a progression of impaired cardiac reserve resulting in increased signs and symptoms of congestive heart failure require an increased dose. This dose is also altered by the degree of congestive heart failure or the complications of cardiac irritable foci, fever, rheumatic activity or increased metabolism. Ambulatory patients commonly do not require as high a dose. Table III gives the various doses for different preparations along with the toxicity levels.

Toxic symptoms include colored vision, headache, nausea, vomiting or diarrhea (the last three are largely reflex from the heart); disorders of the heart mechanism such as ectopic beats, auriculo-ventricular block and others; and changes in the electrocardiogram such as depression of the S-T segment and lowering or inversion of the T waves.

It has been stated that the use of digi-

Table II

PREPARATION	INITIAL DOSE	SUBSEQUENT DOSE	INTERVAL
Ouabain (G Strophanthin)	0.5 mg.	0.1 mg.	Every ½-1 hr.
Strophanthin	0.5 mg.	0.1 mg.	Every ½-1 hr.
K Strophoside	0.5 mg.	0.1 mg.	Every ½-1 hr.
Lanatoside C	1.0-1.6 mg.	0.4 mg.	Every 6 hours
Digoxin	0.5-1.0 mg.	0.25 mg.	Every 6 hours

toxin has greatly simplified the problem of digitalization and it has been advocated for routine oral digitalization. Both digitalis leaf and digitoxin are equal in speed of absorption and elimination but the difference lies in potency. Digitoxin is almost one thousand times as potent.[26] It is believed that digitoxin will supplant digitalis leaf and tincture preparations to such an extent that they will become simply of historical interest.

Digitalis Dosage for Children

Some advocate the modification of digitalis dosage for children as follows: digitalis leaf, oral dose for child of 22.7 Kg. (50 lbs.)—0.1 Gm. as test dose followed by 0.2 Gm. 2 hours later, 0.2 Gm. 8 hours later and 0.1 Gm. 8 hours after that. If at the end of 20 hours digitalization is not complete 0.1 Gm. should be given every 6 hours for 1 or 2 doses and then a maintenance dose set up. Another worker reports that adult doses were given to children with no untoward effects. Another recommendation is a dosage schedule of 0.1 Gm. 3 times a day at 6 hour intervals for 3 days followed by a dose morning and evening (if required) on the fourth day. A maintenance dose of 50 mg. daily for six days a week is then established.[1]

Calcium Synergism

Calcium solutions should not be injected into digitalized patients because of the marked synergism of calcium with digitalis. It has been reported that this synergism results in complete cardiac arrest.

Diuretics

Diuresis is brought about to some extent by digitalis in that it improves the general blood flow as well as that flowing through the kidneys. However, this may not be sufficient to relieve pulmonary or hepatic congestion, edema serous effusion, acute pulmonary edema or nocturnal paroxysmal dyspnea. Therefore it may be necessary to administer a diuretic. In cases where the conditions listed are very severe the diuretic should not be given in the beginning of therapy. If the pleural effusions are copious they should be removed by aspiration at the very beginning so as to make the patient more comfortable and to avoid slow absorption of the fluid into the body. A diuretic is also indicated temporarily to provide symptomatic relief until digitalization is complete. In some cases where the symptoms and signs of myocardial failure are mild a diuretic may be indicated rather than digitalization because the latter would interfere with proper evaluation of cardiac disease, as for example in patients with myocardial infarction digitalization might alter the electrocardiogram. A diuretic is also useful in dehydrating the patient so as to prevent paroxysmal dyspnea.[1,2,9]

Table III

DIGITALIS PREPARATION	MAINTENANCE	TOXICITY
Digitalis leaf or purified extracts	0.1 Gm.	0.2-0.3 Gm.
Digitoxin	0.1 mg.	0.2-0.3 mg.
Digoxin	0.5 mg.	1.0 mg.
Lanatoside C	1.0 mg.	1.5-2.0 mg.
Lanatosides A, B and C, comb.	0.33 mg.	0.66-0.99 mg.
Squill (Urginea Maritima)	0.5 mg.	1.5 mg.
Squill (Urginea Indica)	0.5-1.0 mg.	1.5-2.0 mg.
Gitalin	0.5-0.75 mg.	1.5-2.0 mg.

Zanthine Diurethics

There are different types of diuretics which are of value in this condition: the xanthines, urea and the mercurial diuretics. Of the xanthine group theophylline produces the best effects but has a tendency to cause nausea and vomiting. The dosage for this drug is 0.2—0.3 Gm. 3 or 4 times a day for a period of 2 to 3 days when a rest period of the same length should be observed. Included in this group also are: (a) theobromine calcium salicylate in doses of 0.5 to 1 Gm. 3 times daily; (b) theobromine sodium salicylate in doses of 1 Gm. 3 times daily or every hour for 4 doses daily and the latter repeated at intervals of 4 days; and (c) theophylline ethylenediamine in doses of 0.1 to 0.2 Gm. 3 or 4 times daily.[2,9] Although these are less effective than theophylline they are better tolerated.

Urea

Urea frequently produces better effects

than the xanthine group. It is given in doses up to 60 Gm. daily in the form of a 50 per cent solution in a dosage of 15 to 45 cc. 4 times daily. For palatability it should be chilled and added to chilled grape juice or some other fruit juice. Urea may be given in the form of the following prescription:

Urea	30.0
Acacia powder	12.0
Cinnamon syrup to make	120.0

Sig.: 1 or more teaspoonfuls well diluted.

This prescription contains 1 Gm. per teaspoonful. Urea acts as a nonthreshold substance removing the water with it when excreted by the kidney.[28]

Mercurial Diuretics

Although the xanthines and urea have been used effectively for years their action is not so effective or so definite as is that of the mercurial diuretics. When administered at the beginning of treatment they frequently result in a more rapid recovery. They may be administered orally, intravenously or rectally. There are a number of mercurial diuretics available as follows: (a) Mercurophylline Injection, U.S.P. in 1 and 2 cc. ampules which contains in each cc. 135 mg. of the sodium salt of β-methoxy-γ-hydroxymercuri-propylamide of trimethyl cyclopentanedicarboxylic acid, equivalent to 39 mg. of mercury and 35 mg. of anhydrous theophylline; (b) Mercurophylline in tablet form, enteric coated, each one representing the concentrate of 0.74 cc. of Mercurophylline Injection U. S. P. equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline; (c) The same compound as in (a) and (b) in suppository form, each one containing 0.5 Gm. of a mixture of 20 per cent β-methoxy-γ-hydroxymercuripropyl-amide of trimethylcyclopentanedicarboxylic acid with 80 per cent of the sodium salt, equivalent to 0.2 Gm. of nonionizable mercury; (d) Meralluride sodium in 1 and 2 cc. ampules each cc. containing 176 mg. of the sodium salt of methoxyoximercuri-propylsuccinylurea, equivalent to 39 mg. of mercury and 48 mg. of theophylline (30 mg. anhydrous); (e) Mersalyl and Theophylline Injection, U. S. P., in 1 and 2 cc. ampules containing in each cc. 100 mg. of the sodium salt of mercury-salicylallyl-amide-o-acetate equivalent to 39.6 mg. of mercury and 50 mg. of theophylline; (f) Mersalyl and Theophylline in enteric coated tablets each one representing 80 mg. of mersalyl equivalent to 31.7 mg. of mercury and 40 mg. of theophylline; (g) Mersalyl and Theophylline in suppository form each one containing 400 mg. of mersalyl equivalent to 158.4 mg. of mercury and 200 mg. of theophylline. Theophylline is included in these products for the purpose of reducing the local irritant action of the mercurial in case some of the solution escapes into the tissues.

Administration

The mercurial diuretics are most efficient following intravenous injection. This method causes no pain as well unless the solution leaks out of the veins into the tissues. They may also be given intramuscularly and all 3 described are interchangeable. The initial parenteral dose is 0.5 cc. so as to test the patient for sensitivity or intolerance. This is followed in 24 hours by another dose of 1.0 to 2.0 cc. varying with the severity of the condition and the amount of diuresis needed. Some advise[2] a 1 to 2 cc. dose every 2 to 5 days or 2 to 3 doses of 0.5 cc. daily whereas others[10] recommend that no routine be established but the intervals of therapy be adjusted to the patient's status. It is believed that the smaller and more frequent doses prevent the extreme diuresis and exhaustion brought on by large doses. However, this necessitates frequent intravenous injections which may result in injury to the veins. The injection should be slow and a fine gauge hypodermic needle should be used.[2] The best guide to the use of the diuretic is the weight curve. As the patient's weight becomes constant the diuresis previously produced has ceased and the drug should be resumed. If the patient shows a gain in weight it is an indication that the edema is again forming and the diuretic therapy should be repeated. The desirable status is for removal of the fluid slowly and gradually, thus allowing for better restoration of compensation. It

is wise to avoid excessive diuresis.[10] After injection of the drug diuresis will usually begin within 2 hours and reach a maximum in 8 to 12 hours. The effect rarely lasts longer than 24 hours. Several liters may be eliminated. The best procedure therefore is to administer it early in the morning to avoid disturbing the patient's sleep.[2] If diuresis is not produced by injecting one of the mercurials substitution of another will probably not be of value either. In attempting to bring it on by repeated dosages there may be a risk of mercurialism.[10] Intramuscular injection of the mercurial diuretics is almost as effective as the intravenous route but pain frequently occurs at the site of the injection. This pain is not prevented by the addition of procaine or another local anesthetic.[9]

The mercurial diuretics may be given orally but this method should not be used in place of the parenteral method unless the patient is difficult to inject, requires slow removal of the edema fluid or is not within reach of medical attention when diuresis is necessary. If indicated the diuretics are given orally in doses of 1 to 2 tablets 3 times a day for no longer than 3 days. As soon as sustained diuresis begins the drug should be stopped. Oral administration of mercurial diuretics is particularly of value in patients with an advanced heart disease in whom the edema reaccumulates rapidly.[10, 27] In such cases the drug is given in maintenance doses of 1 to 2 tablets daily. This results in a slow dehydration over a period of 1 to 4 weeks. Acidifying salts may be necessary. Until the oral diuretic becomes effective it may be necessary to administer it parenterally as well in which case it is necessary to watch for possible development of mercurialism, renal failure, or digitalis toxicity due to spontaneous redigitalization. Toxicity may be avoided by stopping the drug for 1 week at intervals of 4 weeks after the patient has been controlled.[10]

The mercurial diuretics may be administered rectally by means of suppositories provided the patient does not have hemorroids. They may produce rectal irritation even in the normal rectum. Because this route is so unpredictable it should not be used unless parenteral and oral routes are impossible. The high content of mercury may lead to mercurialism.[2,10]

Enhancement Effect

Oral administration of ammonium chloride will enhance the effects of the mercurial diuretics. Also used are ammonium nitrate and potassium nitrate. They are given in doses of 2 Gm. 3 or 4 times a day preferably in the form of enteric coated tablets. Some advise giving one of these acid forming salts the day before the diuretic, the day the diuretic is given and for two days afterward.[9] Others[2] also state that they may be used continuously for their slight diuretic affect. Enhancement to as much as 20 per cent is achieved by giving ammonium chloride for 2 or 3 days before the diuretic has been reported. Potassium chloride has also been used but like the other salts is not so effective as ammonium chloride. Ammonium chloride or potassium nitrate may be prescribed in the following forms[1]:

Ammonium chloride	30.0
Anise water	30.0
Glycyrrhiza syrup to make	120.0

Sig.: One or more teaspoonfuls well diluted as directed.

Potassium nitrate	30.0
Glycyrrhiza syrup to make	30.0

Sig.: One or more teaspoonfuls well diluted as directed.

These prescriptions contain 1 Gm. of drug to each teaspoonful.

Urea is also employed to enhance the effect of the mercurial diuretics. Still another drug which may be used to enhance the effect of the mercurial diuretics is sodium dehydrocholate administered intravenously simultaneously with the diuretic.[28] It is injected slowly in doses of 2 Gm. or in 20 per cent solution in doses of 10 cc.[29] One group has reported that a dose of 2 cc. of a mercurial diuretic mixed with 500 mg. of ascorbic acid produced better results.[30] Another authority has stated that the acid-forming salts are unsatisfactory when used alone because they act like saline laxatives at the point where

they are effective in enhancing the mercurial diuretics.[14] However, some people can take large doses without this disturbance.

Although the mercurial diuretics possess a great amount of mercury they do not appear to cause renal damage despite prolonged use. Before administering one of these drugs it is necessary to ascertain whether the presence of albuminuria and casts is due to the renal stasis brought about by congestive heart failure or to a nephritis. It is necessary also to establish that there is no albuminuric retinitis, no marked retention of nitrogenous metabolites in the blood, and no red blood cells in freshly voided urine The specific gravity of the urine should not be fixed at a low level.[2]

Reactions

There is a possibility of certain untoward reactions developing from the use of mercurial diuretics.[31-32] The patient may be sensitive to mercury and thus none of the drugs can be used. Urticaria, rash, chills and fever, sense of tightness in chest and related symptoms are all signs of sensitivity. If the sensitivity is suspected to be only to one certain compound another mercurial diuretic should be used.[28] The presence of an active nephritis, severe anemia, impending uremia, cachexia and ulcerative conditions of the bowels precludes the use of these drugs. If the patient is susceptible to gout excessive diuresis may bring on an attack or may result in acute urinary retention. Care should be taken in patients with prostatic obstruction also.[9, 10] Signs of digitalis toxicity must be watched for because this drug is retained in edema fluid and serious effusions and as diuresis develops the digitalis passes into the blood stream, resulting in a spontaneous redigitalization with the release of sufficient digitalis to cause toxicity. This state may be avoided by decreasing the maintenance dose of digitalis or decreasing the dosage of the diuretic so as not to produce an excessive diuresis. In patients who are on a low salt diet tissue dehydration and depletion of sodium may occur resulting in muscle cramps, weakness, abdominal colic, nausea and vomiting, elevation of temperature and progressive stupor and coma. This should be avoided by giving 5-10 Gm. of sodium chloride daily for several days, adjusting the diet or decreasing the diuretic dose.[1,2,9,10] Mercurialism occasionally occurs and particularly following oral or rectal administration unless the rest periods are observed. It is not usual in parenteral administration unless the drug is given to patients no longer having diuresis. Sudden death rarely occurs following use of mercurial diuretics but has been observed particularly in patients having a sensitivity to the drug if administration is continued. The mercurial diuretics rarely produce any skin disorders but if this does occur another mercurial should be used.

In certain cases it may be impossible to produce diuresis. These include patients with renal failure, in greatly progressed or terminal states, with massive ascites, with hypochloremia, or with hypoproteinemia. Inadequate digitalization or inadequate use of acid forming salts may also be responsible. In patients with advanced heart disease adequate digitalization is necessary to achieve the maximum response to the mercurial diuretics and the acid forming salts are needed for their enhancement effect.[10] The action of mercurial diuretics may be inhibited by depletion of blood proteins or electrolytes or the intake of large quantities of sodium or alkalies. Administration of opiates may slow the diuresis. In some cases it is necessary to mechanically drain the edema or serous effusions before diuresis can be established.[9] In pleural effusion or ascites thoracentesis or abdominal paracentesis may be indicated. In rare cases Southey tubes or multiple scarification may be necessary to relieve subcutaneous edema.[2] If no reason can be established for failure of the drug to establish diuresis a rest period of 2 to 3 weeks should be observed and then the drug injected intravenously. This usually brings on the desired results.

Quinidine

Quinidine was introduced some years ago as being of value in congestive heart failure. However, its use has been controversial[34-38] so that the National Research

Council has set up the following criteria for its use[39]:

1. Ventricular tachycardia diagnosed electrocardiographically.

2. Congestive heart failure that appears definitely to have been precipitated by the sudden onset of auricular fibrillation (if not adequately controlled by digitalis).

3. Persistent premature ventricular contractions in patients who have had acute coronary artery occlusion.

4. Chronic disease of the heart associated with paroxysmal auricular fibrillation, paroxysmal auricular tachycardia or auricular flutter.

5. A history of systemic embolization in a case of paroxysmal or established auricular fibrillation.

When properly used with due precautions the results are striking.[40]

Quinidine is administered orally (the most satisfactory), intramuscularly or intravenously. Orally a test dose of 0.2 Gm. is given and if no reaction develops in several hours 0.4 Gm. is given every 2 hours until the arrhythmia is broken. This dosage may be repeated for 2 or 3 days increasing it each day by 0.2 Gm. Close observation of the patient is necessary and if toxic symptoms develop the drug should be stopped.

In those patients who possess a hypersusceptibility to quinidine nausea, vomiting, convulsions, palpitation, headache, faintness and flushing may occur. In some rare cases auricular fibrillation may be changed to more serious disorders such as intra-auricular block, ventricular tachycardia and fatal ventricular fibrillation. Digitalization some time before administration of quinidine may show better results because the latter is less toxic and depressant to skeletal muscle when it is not overloaded and fatigued.[40a]

After the arrhythmia is broken a dose of 0.2 Gm. is given 3 times daily for 1 week. In cases of recurrence the maintenance therapy is 0.2 Gm. 2 or 3 times daily. When more rapid action is required the drug may be given intramuscularly. The dihydrochloride has been found to have some use in this direction. Intravenous administration is rarely necessary and is dangerous.[40]

Dihydroquinidine

Dihydroquinidine, a derivative of quinidine, has been found to be 20 per cent more effective than quinidine in human auricular fibrillation. Animal studies also showed better results.[40-42]

Fagarine

Fagarine, an alkaloid obtained from trees growing in the Argentine, has shown some value in fibrillation but as yet it is not available in the U. S.[40,43]

Therapy of Accompanying Symptoms

Nausea and vomiting may be caused by passive congestion of the gastro-intestinal tract or liver and may be alleviated by larger dosages of digitalis. If caused by local irritation of the stomach by the oral digitalis preparation this should be discontinued for 4 to 5 days and given by rectal or parenteral routes or digitoxin may be used. If this does not control the condition the patient should be kept from all food and fluid for 24 to 36 hours. Give a cleansing enema followed by a retention enema of chloral hydrate 1 Gm., sodium bromide 2 Gm. in 4 oz. of water. Following this the patient may sip broth, ginger ale, tea or milk and then the diet is again built up based on how the patient tolerates it.[9] Vomiting may result from a reflex stimulation of the vomiting center in the brain following oral or parenteral administration of digitalis so that it may be necessary to stop giving digitalis entirely for 3 or 4 days.

If severe dyspnea or cyanosis occurs or when these symptoms do not respond to congestive heart failure therapy oxygen therapy is indicated and should be continued as long as necessary (3 to 4 weeks in some cases). It may be given by nasal catheter, face mask or tent (most comfortable; concentration should be higher than 50 per cent). It has been reported that heart failure of nonrheumatic origin responds better to oxygen therapy than does that associated with rheumatic heart disease.[44]

Cheyne-Stokes respiration may be greatly increased by congestive heart failure and sleep may be disturbed. This may be alle-

viated by a slow intravenous injection (reduces possibility of headache, thoracic oppression or uncomfortable flushing) of theophylline ethylenediamine in doses of 0.24 to 0.48 Gm. in 20 cc. of dextrose solution. Intramuscular injection may be used but is frequently painful. If given before bed time it usually prevents recurrence in the night. Prevention is also possible by means of rectal administration of a suppository or a solution containing 0.5 to 1.0 Gm. following a cleansing enema. Oxygen or small doses of morphine (8 mg.) or one of the related compounds may be necessary.

Paroxysmal nocturnal dyspnea or cardiac asthma is treated by placing the individual in an upright or semi-sitting position immediately. Morphine (15-30 mg.) and atropine (1-2 mg.) should be injected subcutaneously or intramuscularly. If the patient has not been digitalized this should be done. A dose of 0.5 mg. of strophanthin may be given intravenously if the patient has not had digitalis for at least 4 days. If he has, then 2 cat units of a digitalis preparation should be given intravenously and should be repeated in 2 hours and in 6 hours followed by maintenance doses.

Acute pulmonary edema should be treated with morphine and atropine and rapid digitalization if not done previously. Oxygen, 100 per cent under positive pressure, is also of value. A phlebotomy of 300 to 500 cc. or a bloodless phlebotomy or venous trapping may give rapid relief. A 50 per cent glucose solution may be given in dosage of 50 to 100 cc. intravenously. Theophylline ethylenediamine (0.48 Gm.) may or may not be added to this.

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A Successful Treatment for Menorrhagia, Pelvic Pain, and Cystic Ovaries

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Menorrhagia, pelvic pain, and cystic ovaries form a large portion of the complaints heard in gynecological practice. They may occur singly or in combination. Surgical treatment has been unsatisfactory because of recurrence of the symptoms. In 1945 the author published his results in treating a series of such cases with large doses of diethylstilbestrol (3). This work was based on data published by Hamblen (1) and by Karnaky (2). The present study is a continuation of the former one and represents patients seen in private practice since that time.

Before any treatment is begun a complete investigation of the patient is made to rule out organic disease. If none is found the patient is given 5.0 mg. of diethylstilbestrol (commonly called stilbestrol) orally at bedtime for 20 nights. This treatment is begun at the end of a menstrual period, if possible, to avoid delaying the next bleeding period. Patients rarely bleed while taking 5.0 mg. stilbestrol daily, but do have withdrawal bleeding within 3 to 11 days after stopping the medication.

Menorrhagia

The term menorrhagia is used in its broadest sense to incude excesive flow, prolonged flow and too frequent flow. Thirty-eight cases of menorrhagia were treated by this method. All but two were relieved. These two were curetted and hyperplastic, proliferative phase endometrium was found. Both have remained well following curettement. Some cases were given 10 to 15 mg. of stilbestrol daily, if 5.0 mg. did not control the bleeding within 48 hours. Normal menses followed such a course of therapy in 36 of the 38 cases. Menorrhagia recurred in some patients within 4 to 12 months. A second or even a third course of stilbestrol was then given. There have been no cases which could not be controlled by this regimen except the two described above. This type of therapy offers most to the patient under 40 years of age. It is felt that the ovary is incapable of returning to normal function after this time and that radium or hysterectomy is better treatment for menorrhagia in this older age group.

Pelvic Pain

There were 12 cases in which pelvic pain was the chief complaint. Dyspareunia was almost invariably present. Pelvic examination revealed marked tenderness of the uterus or ovaries or both. In all cases the tenderness and pain disappeared after a 20-day course of stilbestrol. Some patients were relieved in a few days. In others, the tenderness and pain subsided gradually, one taking two months to subside completely. The relief persisted for a varying period after cessation of therapy. Some remained well after two years. Some required a second course of stilbestrol after 6 to 12 months.

Cystic Ovaries

Of 36 cases of cystic ovary, return of the ovary to normal was determined in 33 following the 20-day course of stilbestrol. Pain on the involved side, especially on standing, was common. Dyspareunia was also frequent. The menses were often too profuse or too frequent. The case was included in the cystic ovary group, if the ovary was 4 cm. or more in diameter. The largest ovary was 8 cm. The smaller ovaries of 4 to 5 cm. returned to normal by the end of the 20-day treatment, but the larger ones took 2 to 3 months to return to normal size. Of the 3 cases in which the ovarian enlargement persisted, one refused surgery, one has hyperthyroidism and will be oper-

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Duhring's Disease

Lester Hollander, M.D., F.A.C.P.

Medical Director, Pittsburgh Skin & Cancer Foundation

Duhring's Disease perpetuates the name of a great American dermatologist.

The later part of the nineteenth century was the golden age of medicine. Sparked by fundamental information which physics, chemistry, microscopy yielded, eager men and women applied it to the study of biology and to the behavior of the body both in health and under the influence of disease and thus brought forth concepts new and logical to replace the hindrance-producing superstititons, empiricisms, ill-founded dogma and other autocratic stupidities, which governed medicine.

Thus tremendous gains were made and these became the stepping stones not only of medical practice, but of benefits which accrued for mankind in general. In a sense they were the harbingers of present day Western culture, with its still unbounded possibilities for the improvement of the lot of mankind.

The glory of these men and women, their self-sacrifice, their devotion in search of truth, their infinite perspicacity has been often and well told. Any emphasis which I may give it may only be anticlimactic, except possibly to mention, with pardonable pride, that many members of the American Medical Association were in the very forefront in these endeavors. They not only searched, not only found, but many achieved the accolade of all searchers of truth.

No greater acknowledgement can come to a physician than naming a disease in his honor; by his name, it becomes a kind of monument to him, which, though but conception-carved, is more enduring than statues on rearing horses, than mausoleums or granite shafts, a distinction which riches can not buy.

The naming of a skin disease in honor of Dr. Louis Duhring of Philadelphia was exceptionally well merited. He was a dermatologist of great attainment, an exceedingly kind man, a well read physician and an unerring, methodical observer—a rare, but necessary combination of qualities for the attainment of his type of professional stature.

Dr. Duhring recognized as a disease entity a group of symptoms, which appeared together frequently enough to arouse attention. He described a new disease, one which was unrecognized by all other dermatologists of the world.

To be able to recognize a new disease requires the knowledge of the signs, symptoms, course, consequences, and vagaries of all the previously described concepts of like nature, a task very much out of the ordinary in itself, a task which requires assiduous study, disregard for hours of

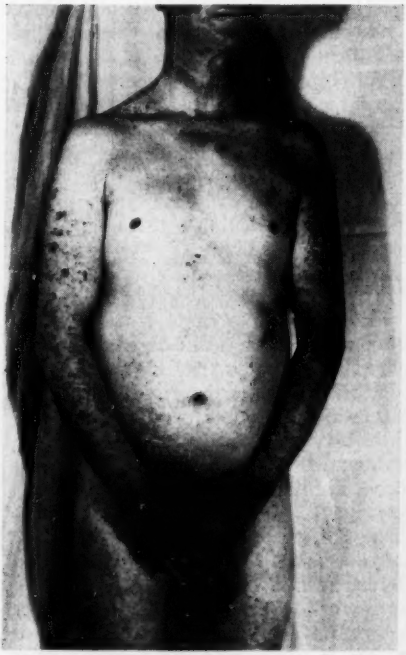

Fig. 1. Typical clinical picture of Duhring's disease.

work, concentration, absorptive cerebration and creative thinking, all of which Dr. Duhring possessed to an unusually high degree.

The skin disease, which he described under the title of *dermatitis herpetiformis,* but which other dermatologists call *Duhring's disease,* is not an infrequent entity. When it appears in its classical form, it is unmistakably unique, but in an aberrant or in a modified form it may be very difficult to identify.

The symptoms of diseases of the skin are divided into two distinctive groups:

1. The subjective symptoms, those which the patient feels or experiences.

2. The objective symptoms of signs, those which others also can perceive.

Itching, burning, pain, tenderness, the sense of something burrowing under the skin, increased sensitivity and its opposite, decreased sensitivity, and the total lack of ability to perceive or to be able to experience the sense of touch, warmth, cold, pain are the subjective symptoms.

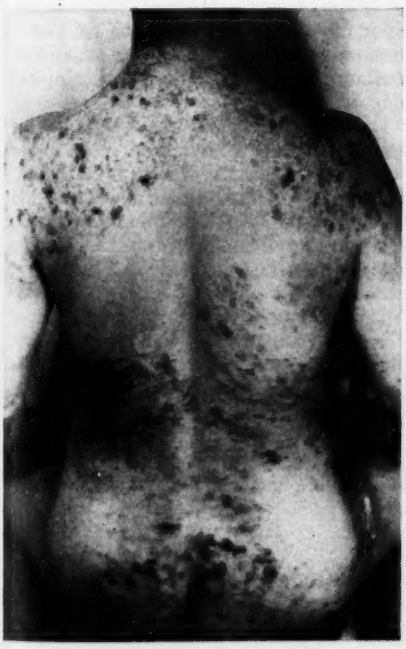

Fig. 2. Same patient as in Fig. 1.

The objective signs belong in the visual and palpatory fields. They are the organic attempts of the skin to tell of any disturbance or misery from which it and, at times, even the other organs suffer.

Actually objective signs are a kind of alphabet designed by the skin for the explicit purpose of describing the fact that all is not well within its boundaries; telling it in a characteristically similar manner under like conditions, the integument hopes that the center of all aggregate information, the brain, will eventually interpret properly the intrinsic story. A universal code has thus been created by the skin, which varies only with the variability of the integument itself.

Repeated recorded observations of these objective signs, observation of their development and eventual evolution, together with other recurring altered phenomena, lead to the correlative knowledge of present day medicine.

Small pinpoint to peasized collections of serum, the saline watery diluent of the body (a reminding remnant of our oceanic existence), occasionally push the outermost horny layer of the epidermis off its moorings and appear in the form of a blister or a vesicle. *A vesicle is the critical objective symptom of Duhring's disease.*

Small groups (ten to twelve) of vesicles superimposed on an area of acute inflammation, such as are not infrequently observed about the lips, constitute the appearance of cold sores, or fever blisters, or the so-called herpes simplex. Since the appearance of Duhring's disease bears a striking resemblance to the above, Duhring, who was a great morphologist, an astute student of form, correctly named the entity *dermatitis herpetiformis,* an inflammation of the skin encumbered by the superimposition of many blister-like lesions.

One can not help but wonder how often he must have sat in a contemplative mood as he read and reread his own notes, his own description of certain patients, who in addition to presenting a terrifically itchy generalized skin disease, also presented other curious groups of brain-nagging simi-

larities, only to say to himself, "I haven't exhausted the study of all the medical journals, of all the case reports, of all the Continental information; if I had, the line on these history sheets reserved for final diagnosis would be completed."

Then came the day when this modest student realized that he was able to decipher a message which heretofore was not legible to anyone else and, in being able to understand these peculiar hieroglyphics of the skin, he unearthed an entity and thus enriched medical knowledge.

Although Duhring's disease occurs at all ages and in both sexes, it is principally a disease of the *adult male* in the fourth, fifth and sixth decade. It usually burns out in the sixties, as a result of natural thinning and drying out of the skin structures.

Friction is the most potent excitant which precipitates attacks of this disease and although the underlying cause for this untoward reaction to mechanical irritation is still to be discovered, a great deal of good is accomplishable if we remember the excitant role friction is capable of playing.

There are some very apt descriptive terms which are applicable to Duhring's disease: bilateral, though not necessarily symmetrical; grouped; peculiarly localized; pigment-producing; scar-forming; chronic; recalcitrant to treatment. All of these succinct characterizations are well deserved as, in most instances, they form the background of this disease.

The classic picture consists of a sparse or diffuse eruption of grouped vesicles on a mildly or severely inflamed skin, and linear and semilunar scratch marks, and usually a few freshly coagulated droplets of blood, just sufficient to make one aware of the principal subjective symptoms: intense itching, which defies all self control against scratching and digging; the eruption does not appear on all skin surfaces as a general rule; a selective distribution which peculiarly localizes the disease on the *stretch* surface of the extremities and the back (also the stretch surfaces of the torso) is one of its characteristics. An unclad patient presenting Duhring's disease, when facing the examiner, will most likely appear to be free of any skin lesions except about and below the knees, but when he turns face about, a totally different appearance presents itself: the side stretch of the arms, the shoulders, the greatest portion of the back, the buttocks, mostly or in part, are covered with the vesicular dermatitis, scratch marks caused by finger nails, brushes, or any other available abrasives, also multiple small boils, the latter being the evidence of secondary infection, which is invariably present as the companion of skin damage caused by scratching. The rounded or oval grouped vesicles, with deposit of pigment throughout the inflamed and normal skin, and various sized rounded and longitudinal depressed scars, two telltale remnants of some previous attacks, are also discernible.

Although less commonly recognized, the *scalp* is not an infrequent site of the disease. Often it is the surface upon which the disease makes its initial appearance. Sharp combs and stiff hair brushes may be the means of creating the exciting cause. Full-fledged generalized attacks may follow such *episodes* of scalp disturbances, especially if unwise topical medication with concentrated scalp preparations has added the insult of chemical irritation to the underlying cause itself.

The word attack appears frequently in this presentation. This is not accidental: I want to emphasize the cyclic, the dynamic nature of this disease. It also tends to explain the fact that improvement or worsening may be an intrinsic quality of it and not necessarily follow any particular medication.

Time has proved the accuracy of most of the original observations made by Dr. Duhring, and as a matter of fact, little new has been added. Studies of the blood, the bodily excretions, tissue chemistry, etc., have been negative, except possibly for the finding that a curious increase in the eosinophiles, the white blood cells, which contain demonstrable eosin stain-attracting granules, exists in certain stages of the attack. No satisfactory explanation for this increase of the eosinophilic leukocytes has been given as yet either in Duhring's disease or as a matter of fact in any other disorder, wherein such increase is found.

For such exists notably in patients infested with intestinal tapeworm and also in one other skin disease: scabies.

There are other similarities which exist between these two skin diseases.

1. Intense itching.
2. Skin damage resulting from scratching.
3. The existence of widely disseminated secondary infection of the skin by a variety of micro-organisms, which normally are kept at extracuticular bay by the natural impenetrability of the epidermal covering.

The changes of location in which these microbes find themselves cause a change in their behavior toward their host, for while on the surface of the skin they were completely harmless, in the deeper layers of the integument they become harmful and disease-producing. This disease is an inoculation pyoderma. It consists of a goodly number of variously sized and widely desseminated boils.

I suspect that this inoculation pyoderma has a great deal to do with the increase of the eosinophilic leukocytes and that this phenomenon is an incident of and related to it, and that the eosinophilia is neither a reaction of this body defense mechanism against the *Acarus scabiei*, the arch criminal causing scabies, nor a mere anomaly in Duhring's disease.

A thesis was put forward that patients suffering from Duhring's disease have a demonstrable sensitivity to iodine, both by ingestion or when it is applied in the form of a patch test. I myself consider it an ill-conceived test, which is neither consistent, nor in any sense applicable, and thus it can have no bearing on the determination of Duhring's disease.

I suppose the question will occur to the reader, can we rationalize the curious distribution of this disease, which usually leaves the face, neck and front of torso free of any eruption even when the rest of the skin surfaces of the body are covered by it?

I believe that a partial explanation can be given. The areas usually affected correspond to the sites of the body most predisposed to friction.

This observation is not merely of academic interest, it is of practical help for the individual endowed with a skin which is so poorly equipped to stand the friction of ordinary daily wear and tear as the one under discussion. It is because I believe that it is of highly practical value that I wish to present it to the readers of this medical journal.

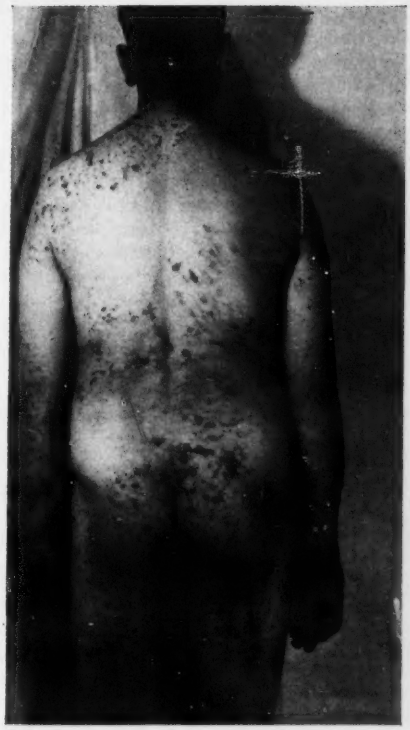

Fig. 3. Same patient as in Figs. 1 and 2.

In the maze of the eruption which Duhring's disease presents, when it is fully blown, not only the areas of predilection, but most of the other skin surfaces, become involved, after it is subjected to polytherapeusis of external and internal variety, by self medication and by genuinely friendly advice, which may include almost anything in and out of the Pharmacopeia old and new, and mostly without much eradicative help.

It is hard to conceive that a simple measure, the reduction of friction dam-

age, can influence this disease and even be instrumental in its eventual cure. Strange as it may seem, this is true, if the principle which it involves, in all its ramifications, is applied with intelligence and appropriate diligence.

There is an almost endless list of activities which is associated with friction: the use and abuse of combs and hair brushes, the act of contemplative head scratching, other semiconscious diggings with pencils or hairpins, the wearing of starch-stiffened linens, the use of rough bed sheets, Turkish towels, rubdowns, body massages, trouser legs, chairs, lounges, even the swing of the body when walking, golfing or other athletic activities, during certain occupational endeavors and many others in similar and foreign fields.

I believe that with a purposeful effort and just a little more than the ordinary care friction damage is reducible to an appreciable measure and to a considerable benefit. It will necessitate, for instance, the wearing of thin, soft, long sleeved and long legged underwear, patting rather than rubbing when drying after a bath, selection of soft and yielding materials as chair and sofa covers, all simple things, but so often very important.

Once the diagnosis of Duhring's disease is established, other than the above suggested treatment requirements are dependent on the complexity of the multiform symptoms which present themselves. These may be tabulated under the headings:

1. Alleviation of itching.
2. Combating secondary infection.
3. Reducing the inflammatory reaction of the skin.
4. Protection from friction.

There are many and widely varied measures suggested to meet these requirements. The following are some which I have used with more than indifferent results. For the alleviation of itching I prescribe a preparation which consists of 1/8 to 1/4 per cent of menthol, salicylic acid and benzoic acid in an equal amount of alcohol and water. The patient is instructed to apply this without rubbing, without friction, on small areas at a time. A fair amount of burning is usually experienced immediately on application, but soon this changes to a pleasant cooling sensation and when this happens another area may be treated similarly until all the itchy parts are covered. It is very important to remember not to cause any friction with this application.

Autohemotherapy, a procedure which consists of withdrawing ten to twenty cc. of the patient's own blood and reinjecting it into the deep muscles of the gluteal region once or twice a week, is also of value.

Itching may also be reduced by the administration of one of the new antihistamine preparations. Fifty milligrams of any one of the several proprietary antihistamines now on the market once every four hours usually is of considerable antipruritic value. As these preparations occasionally cause sleepiness as a side effect, it is important that they be not taken when automobile driving is contemplated.

"Nerve medicines" and sleeping potions act in a detrimental fashion and should not be given.

To combat secondary infection sulfapyridine in small doses in combination with sodium bicarbonate is of value. At times the powerful guns of penicillin by the intramuscular route at hourly intervals may serve the needed purpose.

To soothe the inflamed skin surfaces and at the same time to reduce friction damage a zinc oxide-starch paste or a bentonite-based petrolatum jelly combination may be used with advantage. When reapplication is needed at twenty-four to forty-eight hour intervals, it is important to remember that the less rubbing, the less effort devoted to the removal of the paste, the better the patient will fare.

Protection from friction, during the attack and after the skin has resumed a normal appearance, is thus a fundamental principle.

The more we consider Duhring's disease, the more we realize the importance of the contribution Dr. Louis Duhring made to the study of dermatology.

631 Jenkins Building.

CASE REPORTS

Marked Hypoprothrombinemia with Hemorrhagic Manifestations Due to Acetysalicylic Acid—Report of a Case

Bernard Farfel, M.D.
Houston, Texas

Acetylsalicylic acid is taken by some people some of the time, by many people a good deal of the time, and by very few individuals at no time. Considering how rarely a toxic effect is reported, one must continue to consider it a safe drug. It is well to recall, however, that sometimes it may cause serious side actions or endanger life.

Nievert (1) and Singer (2) have pointed out the role acetylsalicylic acid may play in causing late posttonsillectomy hemorrhage. Nievert used acetylsalicylic acid in combination with synkavite, a vitamin K-like substance, to overcome this effect. The hemorrhagic tendency was ascribed to hypoprothrombinemia. A study of the administration of sodium salicylate was done by Butt (3) et al., who reached the conclusion that no deleterious effect on the liver parenchyma resulted, but continued high dosage of sodium salicylate led to a prolonged prothrombin time. Rappoport et al. (4), reported a case of fatal thrombocytopenic purpura due to administration of sodium salicylate.

In this following case report, it will be shown that aspirin caused a severe hypoprothrombinemia. The danger of such a condition is evident. The possible value of inducing a hypoprothrombinemia should also be considered.

Case Report:

H.B., a 49-year-old white male, a used clothing merchant, was seen March 9, 1947, with the chief complaint of hematuria. The hematuria had apparently existed for several days. Further history was elicited of bleeding from the gums, melena, and skin purpura for the past several months. Past history included a left inguinal herniorrhaphy and usual childhood diseases. For many months patient has been troubled with headaches, and has been taking about 30 grains of aspirin daily. Family history all non-contributory. Father died of cancer, original site not known. The patient was admitted to the St. Joseph's Infirmary that night, March 9, 1947. Physical examination revealed a white male, well nourished, appearing acutely ill. The fundi were negative. There was oozing from the gums. There were many small, easily bleeding nicks on the face from shaving. Chest findings were normal. Blood pressure 128/84. Regular sinus rhythm 84 per minute. Examination of the abdomen revealed no masses, tenderness, nor enlargement of liver or spleen. Extremities showed no petechiae or edema. Temperature on admission 99.6.

Laboratory findings were as follows on March 9, 1947, and on March 10, 1947: Urine negative except for gross hematuria. Hb. 8.4 Gm. (59%). Coagulation time 6 minutes 30 seconds, bleeding time 2 minutes, red blood count 3,250,000, white blood count 9400, platelets 104,000, 76% neutrophiles, 4% eosinophiles, 20% lymphocytes, prothrombin 17% of normal, clot retraction 18 hours.

The patient was receiving aspirin in the hospital until March 11, 1947, when it was discontinued. He was also receiving vitamin K and vitamin C. On March 11, 1947, his stool was positive for occult blood. His vitamin K and C therapy was continued and a transfusion of 500 cc. of citrated blood given.

March 13, 1947, icteric index 7.4 units, cephalin flocculation test negative and clot retraction in one hour. On March 14,

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MISCELLANY

This World Today

By Royce Brier

One of the most amazing phenomena of modern times is occurring in Moscow in the Battle of the Scientists.

This is quite different from the Battle of the Artists, of which the humiliation of the Russian composers earlier in the summer is an example. Art is a matter of taste, within limits. You may not like scratchy noises or the scrambled egg mood of so-called modern art, but some folks manifestly do.

If Uncle Joe and the Politburo hearties don't like the way Comrade Shostakovitch puts one note behind another, complaining it is derivative of bourgeois decadence, that is a matter of taste. Music critics in the year 2000 may have a low opinion of what the Politburo insists is healthy Russian music in 1948, and that will also be a matter of taste.

But science isn't a matter of taste. Science is a search for the true, and a relinquishment of the false in the universal environment. It is conceded there exist in science large areas in which the true and the false cannot be immediately determined. Scientists hold conflicting views on this or that theory, process or state. But there are large areas on which most respectable scientists are agreed. No scientist doubts the earth is a sphere, though it hardly looks like one.

Further, determination of the true and the false in science can only be made by scientists. For one untrained in some field of science to determine the true or the false in that field, is as silly as for one who has never studied the violin to undertake to play the Brahms Concerto.

You would think that after the Galileo affair the politicians would be chary, seeing even politicians now acknowledge the Copernican system, but such is not the case.

A few days ago the Soviet Academy of Sciences liquidated a biological laboratory, and relieved of their duties two internationally known biologists, L. A. Orbelli and I. I. Schmalgausen.

The Academy director then sent a letter to Stalin saying the Academy would "correct its mistakes . . . clear the path for the development of the advanced Soviet science in the name of the great purposes of our people, and in the name of the victory of communism."

Back of this item is an incredible situation. Something over eighty years ago an Austrian botanist named Mendel, engaged in genetic experiments with plants, devised a set of laws relating to the descent of characteristics (color and form) from ancestor plants. Subsequent investigation confirmed that the laws prevailed throughout organic nature about as Mendel had formulated them, and established the importance of heredity whether in plant, fish or men.

Very few scientific determinations have had more widespread acceptance in our century among those qualified for judgment. This was a turning-point in a long-standing controversy over the comparative importance of heredity and environment in the transmission of characteristics, and environment lost importance in inverse ratio as heredity gained.

But note that this is, in its quaint way, anti-Marxist, or at any rate, anti-Politburo, for the Politburo is dedicated to the belief that environment (in its case, a socialist environment) will make new men and a new society. Therefore, the Politburo cannot concede that Ivan is a creature of heredity, as Mendel found his peas to be, for that would get Ivan to thinking maybe his environment is not so important as he is being daily told it is.

This is not, however, a new battle, joining after the battle with Hitler ended. Ten years ago an eminent geneticist, one Vavilov, after long experimentation, held with Mendel that primarily environmental characteristics are not transmitted from generation to generation.

What happened to Comrade Vavilov's deviationist rabbits or mice, as the case may be, is not known, but what happened

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EDITORIALS

Combating Malaria A Top-Priority Program

The two papers on malaria in this issue, one presenting research and one bedtime therapy, are timely and enlightening in an era which is witnessing this disease's attack on "one hundred million persons a year," a disease which is "one of the chief contributing causes of the world food shortage since it strikes at the heart of the world's agricultural areas in the tropics and subtropics."

Good Nutrition Versus Hospitals

Doctor N. Philip Norman thinks that that segment of our knowledge which has proved the relation between foods of quality and good health (*J. of the Amer. Academy of Applied Nutrition,* vol. 2, no. 1, 1948) is slighted by our "chaotically disorganized and confused food culture and economy." There is a rise in all forms of degenerative, mental and nervous diseases and of oral pathology at the same time that better trained professionals (doctors and dentists) apply the advances of science. Also there is to be noted the growth of medical centers, hospitals, clinics and custodial institutions. The Government itself is establishing a great chain of hospitals at vast cost.

What goes on here? What is the trouble?

Norman does not think the answer lies in more and more professional and institutional care but rather in an abundance of foods of quality. He declares that "when politicians, statesmen, and professionals become imbued with the perspective that all of these huge hospital and clinic expenditures could be drastically reduced by the simple expedient of enacting a dynamic, intelligent food and drug law to completely revolutionize and delete most of the processing units of the food industries, then a new era in public health will be born."

In so far as Norman's understanding of the situation is sound, it seems to offer a number of solutions to our sickness problem. To him it throws light on why, among other efforts, we have frantic drives for funds to combat the huge back-log of illness and to repair the mechanisms of an obsolete (?) hospital system.

Of course, State medicine of the sort now being propagandized would not affect the system whereby "these spurious, processed food products, spawned in industrial laboratories, are sold to consumers." Things would remain as under the present order; neither dispensation holds any hope in itself; reform must cut under present and possible future orders deeply.

Booz, Allen and Hamilton, New York, Chicago and Los Angeles experts in the management problems of institutions, submit some interesting views concerning hospitals which may have a bearing upon this problem of good nutrition. They point out how they have been obliged to restrict expansion, rebuilding and services while the demand upon their facilities has grown more than 500 per cent in the last eight years. The cost of goods and services has risen 60 per cent higher than the prewar figure. While rates have risen salaries and wages have also spiralled. Meanwhile federal estate and gift taxes and state inheritance taxes have eaten away the large fortunes that were once the mainstay of private institutions. "The income tax laws put a damper on the accumulation of new fortunes on which private agencies may draw. For example, individuals earning over $100,000 in 1929 retained an aggregate net income after federal taxes of $3,717,000,000. In 1945, the latest year for which complete figures are available, those in the same bracket had a total net income after federal taxes of only $453,000,000, less than one-eighth the 1929

figure."

If the national nutrition were what it should be, perhaps the seriousness of the hospital situation would be greatly mitigated; not so many hospitals would be needed and the maintenance of those giving necessary service assured.

But right now we are allegedly drowning in the full tide of phony food—and fatuously relying upon synthetic vitamins.

Changing Sex Standards

It has been pointed out that the effect of unchastity on the nervous system may be severe. "Such relations are clandestine, furtive, full of fears. This leads to neurosis." But in a recent issue of the *New York Times* a staff writer says that "Kinsey's study has undeniable value . . . . as a sort of instrument for mass psychotherapy for the removal of feelings of guilt."

With the feelings of guilt dissipated, neurosis from this source will presumably be abolished. Let us grant that conscience, in this sphere of life, will then no longer make conscientious persons of us all—but the idea that getting rid of this type of neurosis closes all the other roads to human disaster related to unchastity is naive, to say the least.

Does not much of this business align itself with conscienceless Communist ideology and action—unscrupulousness in attaining ends; temporary expediency in the making of treaties; the sanctioning of lies and general deceit; the imposition of slave labor; the use of starvation as a weapon against innocent people; disregard of decent considerations, human and social? The Communists suffer no feelings of guilt in such matters and doubtless lack neuroses due to such factors and to chastity. But who honestly believes that such an unprincipled way of life does not lead to ultimate disaster?

Meet Munchausen, Jr.

In our June 1948 issue, writing editorially about "Kinsey on the Male," we suggested that certain fallacies of the solemn and earnest author may grow out of the spoofing to which he has almost undoubtedly been subjected. We instanced an individual who, though really impotent, compensates for his deficiency with "tall tales." The tallness of the tales is frequently a measure of the degree of deficiency.

At this writing there occurs to us the Kinsey male who allegedly had thirty orgasms a week for thirty years.

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MILESTONES IN MALARIA

—Concluded from page 469

sistence of this exo-erythrocytic cycle in the liver after the establishment of blood infection.

We can now summarize this recent knowledge as follows:—The inoculation of sporozoites from infected anopheles is followed by the development of the pre-erythrocytic cycle within the parenchyma cells of the liver and in this plasmodial mass small segmenting forms (cryptomerozoites) are produced and on entering the bloodstream produce a clinical attack of malaria; not all of them do so, however; some enter normal liver cells and repeat the process again and again, irrespective of whether the blood cycle (erythrocytic cycle) continues or not, in the face of therapy with quinine or of naturally-produced immunity which destroys the cryptomerozoites the moment they enter the bloodstream. The exo-erythrocytic forms are protected from this destructive action by reason of their position within the liver cells, but when the active immunity of the human body is impaired this is no longer active and the cryptomerozoites again enter the bloodstream and produce a clinical relapse.

Thus it will be readily understood, allowing for the complexities of the scientific terms, that all these accumulated facts have a definite bearing on treatment, and that our standards for an entirely satisfactory antimalarial drug will be based upon its ability to destroy the exo-erythrocytic stages of the parasite within the parenchyma cells of the liver.

149 Harley Street

Foreign Letter—London

Blood Products Research in Britain

Margaret Mackay

Member of the staff of the Blood Products Research Unit of the Medical Research Council (Great Britain).

The filtration unit at the Lister Institute of Preventive Medicine, London, is once more fractionating plasma after having suspended this process since 1943. The need then was for dried plasma, and fractionating had to take second place.

It was in 1942 that the staff of the Institute began producing a special form of transfusion fluid made by removing fibrinogen and unstable lipoproteins from plasma with ether at low temperature. Then in the autumn of 1943 the filtration unit was established at the Lister Institute by Britain's Medical Research Council, to prepare Seitz-filtered human plasma to be dried at Cambridge. In the same year the need for dried plasma became so acute that it was decided to abandon the more elaborate process until after the war, though some purely experimental work continued.

It was about the same time that E. J. Cohn developed the ethanol fractionation of human plasma at Harvard, United States, and made possible the use of certain of the plasma proteins in clinical work. Supplies of fibrinogen, fibrin foam and thrombin were generously made available to surgeons in England, and were so valuable that their production became necessary.

The Harvard process demanded a specialized equipment which was not available in 1944. The separation of plasma proteins by ether apparently offered less scope, but the fraction most urgently needed, fibrinogen, could be precipitated by ether, and as the apparatus was available, the method was examined in the hope that it could be extended to other proteins. Experiments showed that fibrinogen could be obtained sufficiently pure, and in a yield good enough to make the process economically practicable. Thrombin could also be prepared, and by a further modification immune globulin may be precipitated from the plasma remaining after the precipitation of prothrombin.

In 1945, fibrinogen, fibrin foam and thrombin became available for clinical trials. The filtration unit at the Lister Institute was expanded, and in 1946 the Blood Products Research Unit came into operation in its present form.

The Unit has retained the double function of the earlier organization. Plasma proteins are prepared and issued to surgeons; blood plasma is bottled and dried. The routine production is financed by the Ministry of Health as part of Britain's National Blood Transfusion Service. Research on the more fundamental properties of the plasma proteins and the development of new techniques is carried out in conjunction with the biophysics department of the Lister Institute.

Dried Plasma for Transfusion

The plasma to be dried is drawn from two London and ten regional blood depots. Blood not required for whole blood transfusion is allowed to stand in a refrigerator until the red cells have sedimented, and the supernatant plasma from 10 pint bottles is aseptically pooled in an 80-ounce bottle. Plasma from blood of all blood groups is pooled together to absorb agglutinins and make it a safe transfusion to people of all blood groups.

The plasma, sent by road or rail, is tested for sterility on its arrival and is stored again in a refrigerator. Any bottles which have become contaminated are discarded, and from the sterile bottles 400 cubic centimeter quantities are syphoned into transfusion bottles, and a second bacteriological test is made to make sure that any plasma infected during the original

sampling or during the syphoning may be removed. This sample is tested for aerobic and anaerobic bacteria.

The transfusion bottle is covered with a drying cap consisting of a layer of cotton wool between two layers of gauze. This cap will let water vapor out during freeze drying, but will prevent the entrance of bacteria, and is covered again by cellophane during storage.

The plasma, after syphoning, is cooled at 3 degrees centigrade for 12 hours and then spun frozen. The bottle of plasma is rotated on its vertical axis at 700 revolutions a minute in a current of air at minus 24 degrees. The plasma is thrown against the sides of the bottle in a layer and will first supercool and then freeze in small crystals. A clear cone will be left down the center of the bottle, increasing the effective drying area. Plasma is then dried from the frozen state. There is a primary desiccation for two days at a presure of 0.02 millimeters of mercury and a temperature of minus 20 degrees. This is followed by a secondary desiccation in vacuum over phosphorus pentoxide at room temperature. The bottles are then capped, filled with nitrogen, and sealed. This material contains less than 0.1 per cent of moisture and will be found to be perfectly soluble after years of storage.

The preparation of fibrinogen is as follows: the blood is taken into a 3 per cent solution of trisodium citrate in the proportion of 440 cubic centimeters of blood to 100 of citrate. The plasma is removed from the red cells by centrifuging at 0 degrees within 48 hours and is passed through a paper pulp filter to remove residual cellular material. It is cooled to minus 0.5 degrees when 11 volumes per cent of ether are added with constant stirring. The fibrinogen separates out, and if it is left in an icebath at 0 degrees will sediment in 12 hours. The supernatant may be removed by syphoning and the precipitate is centrifuged to remove occluded plasma. It is then intimately mixed with citrate saline containing 8 volumes per cent of ether. It is again centrifuged and the washed precipitate is disolved in a volume of citrate saline one-tenth that of the original plasma volume. The solution is warmed to 25 degrees, Seitz-filtered and then dispensed in 10 cubic centimeter quantities and dried from the frozen state. From 30 bottles of blood, 60 to 70 ampoules of 10 cubic centimeters may be obtained, and the final solution will have a protein content of 2 per cent, of which 85 per cent is fibrinogen and 15 per cent other serum proteins.

Making Fibrin Foam

Fibrin foam is made by mixing fibrinogen with air by spinning a metal disc in 150 cubic centimeters of fibrinogen solution at 2,000 revolutions a minute for 30 seconds and then adding one half unit of thrombin for every cubic centimeter of fibrinogen. The fibrinogen-thrombin mixture is poured into a sterile tray covered with a drying lid and is frozen to minus 24 degrees and dried from the frozen state. The dry foam is dispensed into glass containers, and baked at 130 degrees for three hours, after which the containers are capped and sealed. The resultant material is a tough and elastic sponge, and when filled with thrombin solution may be used as a haemostatic in surgery. From 16 liters of plasma about 100 to 120 bottles of foam may be made.

Thrombin, which is used with both fibrinogen and fibrin foam, is prepared in the following manner: the plasma remaining after the precipitation of fibrinogen is made slightly acid by the cautious addition, with stirring, of 11.5 volumes per cent of 4.15 per cent citric acid at 0 degrees. In the presence of ether prothrombin will come out of this solution and sediment in 12 hours. The supernatant is syphoned off the precipitate, which is centrifuged and twice washed with distilled water; it is then dissolved in citrate saline so that the final volume is one-tenth that of the original plasma volume. The prothrombin thus obtained is converted to thrombin by neutralizing the solution, then adding calcium and placental thromboplastin. The solution obtained contains 150 to 200 thrombin units per cubic centimeter which, although not of a high degree of purity, has been found satisfactory clinically.

Fibrin foam and thrombin have been

found invaluable in neurosurgery and have been used successfully in lung surgery. The chief use of fibrinogen, again in conjunction with thrombin, has been in skin grafting although it is used also in lung and ophthalmic surgery. The quantities of material are still limited, and it has been found necesary to restrict its use to those fields where it will be most useful, although that field is continually extending.

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A SUCCESSFUL TREATMENT FOR MENORRHAGIA

—Concluded from page 491

ated when the thyroid is under control, and the third was operated. She had had bilateral 6 cm. masses in each of the adnexa. The right subsided, but the left remained large and painful 5 weeks after the end of stilbestrol therapy. The patient was 39 and insisted upon surgery for relief. The sigmoid was found adherent around a subsiding hemorrhagic cystic ovary. The right ovary also showed small hemorrhagic cysts although it was normal in size. The author was influenced by another patient, previously reported, who had had bilateral ovarian cysts 7-8 cm. in diameter, to operate upon her for residual pain after 2 months when the ovaries had returned to normal size. In this case the ovaries were grossly normal at surgery and were not molested. There was no pelvic pain after the patient left the hospital.

Persistent pain in the right lower quadrant of the abdomen often leads to the removal of the appendix for "chronic appendicitis." The author feels that chronic appendicitis occurs rarely, if at all. Pain attributed to the appendix in the absence of other signs of appendicitis is usually due to a tender or to a cystic ovary. (It is assumed that urinary tract infection has been ruled out.) The stilbestrol treatment described in this paper relieves such pain.

Summary

1. A second series of 86 cases of menorrhagia, pelvic pain and cystic ovaries is presented.

2. The successful control of such cases by means of a course of 5.0 mg. stilbestrol daily for 20 days is described.

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THIS WORLD TODAY

—Concluded from page 498

to Vavilov is known. He got the gate. One Lysenko got his job, and if the little laboratory critters are still transmitting characteristics by heredity, and disregarding their socialist environment and the dictate of the Politburo, Comrade Lysenko is not one to bring that up. Neither is a colleague, a Prof. Zhdanov (not to be confused with the late statesman), who recently wrote Stalin in effect that scientific validity is not established by experimentation, but by political authority.

Have you ever heard of any nonsense so sheer as this? Here is a group of politicians, who wouldn't know a gamete from a zygote. But they have a dialectic, and all human knowledge must conform to it. That includes Nature. If she doesn't conform, change her laws so she will conform.

So if a communist white rabbit and a bourgeois black rabbit have a litter, and they all turn out white, that's dandy. But if one of the offspring has a litter, and they turn out two white, two black and two black-and-white, showing the taint of grandpop's blood, why, report them all white. It's a Soviet laboratory, ain't it, and Soviet rabbits are white, and no sass from you, Comrade!

Don't think Br'er Rabbit is worrying about it, though. They can send him to Siberia and he'll love it, and continue to produce little rabbits by Mendelian law.
—Reprinted by courtesy of the *San Francisco Chronicle.*
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CONTEMPORARY PROGRESS

MEDICINE

Evaluation of the Newer Therapy of Ulcerative Colitis

J. A. Bargen *(Southern Medical Journal,* 41:646, July 1948) reports that at the Mayo Clinic from January 1, 1946 to July 1947, a diagnosis of streptococcic ulcerative colitis was made in 489 cases. In twenty-five years before 1940, approximately 4,000 patients at the Clinic showed ulcerative colitis of this type. In this same period, there were only 140 patients with the segmental type of colitis, about 500 patients with ulcerative colitis of unknown origin, 200 patients with tuberculous colitis, 1,200 with amebic colitis, 50 with chronic bacillary dysentery and 50 with the lymphopathia venereum type of the disease. In the diagnosis of ulcerative colitis, the stools, or rectal discharges, must be examined both grossly and microscopically. In streptococcic ulcerative colitis, the stools are bloody, mucoid, purulent and contain large numbers of streptococci. Proctoscopic examination should always be made, as must of the lesions occur in the distal segments of the bowel that can be visualized by the proctoscope and sigmoidoscope. The roentgenologic examination should be made last. If a fulminating form of streptococcic ulcerative colitis is present absolute rest in bed is essential; in this severe phase of the disease, fluids should be given intravenously and protein should be supplied by a preparation containing all the essential amino acids or by blood plasma; nearly all these patients also require one or more blood transfusions. Extra vitamins are also needed, especially B complex, C and K. Until the patient can tolerate sulfonamides by mouth, sulfadiazine is given intravenously; for oral administration "neoprontosil" or phenylsulfathiazole is most satisfactory. Penicillin is also given intramuscularly. When the severe fulminating phase has passed, the diet must be increased cautiously to approximately 2000 calories daily with adequate protein, and later to about 3,500 calories with at least 140 Gm. protein daily. During this less severe stage anticolitis streptococcic vaccine in subreaction doses is of value. In some cases of streptococcic and other forms of ulcerative colitis, tincture of iodine has been used as an aid in controlling diarrhea and other active symptoms. The dosage employed is 10 to 14 minims of a 7 per cent tincture of iodine in a glass of water after meals, for a week at a time, or occasionally, even longer. In some cases of chronic streptococcic ulcerative colitis, a salicylate has been of benefit; and recently a group of Swedish workers have prepared a substance combining a salicylate and sulfapyridine, which the author has used in 8 cases with favorable results. Operation is usually indicated in ulcerative colitis only if complications are present; in the segmental type of the disease, however, surgical resection of the diseased segment is often necessary. In ulcerative colitis of unknown origin, the treatment is much the same as in streptococcic ulcerative colitis; but the response to treatment is usually not so satisfactory, and ileostomy is necessary in a larger percentage of cases. In amebic colitis, treatment with emetine hydrochloride and carbarsone concomitantly, followed by one of the iodide preparations, gives the best results. In chronic bacillary dysentery treatment is much the same as in streptococcic ulcerative colitis; phthalylsulfathiazole is probably the sulfonamide of choice,

which may be combined with sulfadiazine.

COMMENT

An excellent presentation for the treatment of severe cases. Diet and psychosomatic medicine are important factors in any case of ulcerative colitis. ***M.W.T.***

Penicillin in the Treatment of Diphtheria and the Diphtheria Carrier State

J. D. Crawford *(New England Journal of Medicine,* 239:230, Aug. 5, 1948) reports the use of penicillin in the treatment of diphtheria and the diphtheria carrier state in a United States Army Hospital in Germany in the last six months of 1946. At this time diphtheria was constantly at epidemic levels. As a control of the effectiveness of penicillin in the treatment of diphtheria, 50 cases of diphtheria treated at the Hospital in the six months prior to the use of penicillin were analyzed. The average period of hospitalization in this group was fifty-seven days; 18 per cent were hospitalized for over six weeks because of minor cardioneurologic complications; 6 per cent were evacuated to the United States because of more serious complications; there were 3 deaths, a mortality of 6 per cent. Omitting these three categories, the average period of hospitalization increased to sixty-one days; but 57 per cent were held in the hospital beyond the six weeks' period because they continued to harbor virulent diphtheria bacilli in the nasopharynx, although free from symptoms. Penicillin treatment for the carrier state was tried in 20 of these patients. Local nose and throat sprays of penicillin were found to be ineffective in the treatment of these carriers; parenteral administration of penicillin in a dosage of 40,000 units every three hours for twenty-five doses also did not give satisfactory results. Parenteral administration of 20,000 units of penicillin every three hours for fifty doses gave excellent results—87 per cent of the carriers so treated becoming negative. During the last six months of 1946, 45 cases of acute diphtheria were treated with a single dose of diphtheria antitoxin (average 60,000 units) and penicillin—the usual dosage being 20,000 units every three hours for seven days or longer. The average length of hospitalization in these cases was forty-five days, as compared with fifty-seven days in the control group. One patient was held in the hospital beyond the six weeks' minimum because of minor cardioneurologic complications (2:2 per cent as compared with 18 per cent in the control group); 2 patients (4.4 per cent) were evacuated to the United States because of more serious complications. There were no deaths (as compared with a 6 per cent mortality in the control group). Omitting the complicated cases the average period of hospitalization was forty-three and one-eighth days; only 3 patients were held beyond three weeks because of the carrier state (approximately 9 per cent as compared with 57 per cent in the control group). In this period 52 chronic carriers of diphtheria bacilli were treated; of 44 carriers given penicillin parenterally (20,-

of the "penicillin failures" and 7 others not treated with penicillin were subjected to tonsillectomy; all became negative except one who required a second course of penicillin. One carrier who failed to respond to the first course of penicillin was rendered negative by a second course. It is concluded that penicillin is a valuable adjunct in the treatment of diphtheria and the carrier state, but does not supplant the use of antitoxin in the acute stage or obviate the necessity of surgical treatment of a small group of carriers.

COMMENT

One wonders how penicillin in oil, 300,000 units daily, will control such conditions.

M.W.T.

Preliminary Report on the Beneficial Effect of Chloromycetin in the Treatment of Typhoid Fever

T. E. Woodward and associates *(Annals of Internal Medicine:* 29:131, July 1948) report the use of the new antibiotic Chloromycetin in 10 cases of typhoid fever. Chloromycetin has been used chiefly in the treatment of epidemic typhus and scrub typhus—both rickettsial infections—with good results. It was during the study of the chemotherapeutic value of Chloromycetin in scrub typhus on the Malayan peninsula that the authors found many cases of typhoid fever, especially in the native population. Typhoid fever in this area tends to be of a clinically severe type with persistence of fever for six or seven weeks. Chloromycetin was used in 10 cases in which the diagnosis of typhoid fever was confirmed by a blood culture positive for *Eberthella typhosa.* In these cases Chloromycetin was given by mouth; the initial dose was 50 mg. per kilo body weight; then 0.25 Gm. was given every two hours until the temperature was normal, and then every three hours for the first five days of normal temperature; the average total dose was 10.1 Gm. There was no clinical evidence of toxicity in any case. In most of these 10 cases in this series Chloromycetin therapy was begun on the tenth day of the disease. Evidence of lessened toxemia and improved general condition was evident within twenty-four hours after treatment was started; in the first 7 cases, the temperature was normal after three days' treatment. In the 10 cases, the mean duration of fever after beginning treatment was 3.5 days. In 8 of the 10 cases blood cultures were made daily for five days after beginning Chloromycetin therapy, and all were sterile. No patient was discharged uutil three consecutive stool cultures were negative. Two of the 10 patients developed relapses with bacteremia after afebrile periods of ten and sixteen days respectively; these recurrences responded promptly to a second course of Chloromycetin. Serious complications developed in 2 other patients—intestinal perforation on the second day of normal temperature in one case and massive intestinal hemorrhage on the fourth day of normal temperature in the other case. Supplementary therapy with streptomycin and penicillin in the first case and whole blood transfusions in the second case resulted in recovery. Eight cases of typhoid fever of a similar degree of severity not treated with Chloromycetin served as controls; one of these patients died of the disease on the seventeenth day. The average duration of fever in the other 7 cases was thirty-five days. The authors conclude that Chloromycetin has a specific therapeutic effect in typhoid fever but the optimum dosage schedule has not yet been determined.

COMMENT

One great advantage of chloromycetin is that it can be given by mouth. A large amount of the weight of chloromycetin is nonionic chlorine.

M.W.T.

Hemophilia: Current Theories and Successful Medical Management in Traumatic and Surgical Cases

Claude-Starr Wright and associates *(Journal of Laboratory and Clinical Medicine,* 33:708, June 1948) report that in their study of 43 patients with hemophilia in the last seventeen years, the greatest advance has been made during and after World War II owing to the chemical partition, isolation and therapeutic study of particular fractions of blood plasma. The

prolonged coagulation time of the hemophilic patient can be controlled so that patients with hemophilia may undergo surgery with safety, by intravenous or intramarrow administration of fresh whole blood or plasma, frozen or lyophilized plasma processed immediately after withdrawal of blood from the donor, or the plasma fraction I of Cohn, recently separated. The latter has proved a potent antihemophilic substance in the authors' experience.

COMMENT

It is a real advance in medicine that surgery can be performed on patients with hemophilia.

PUBLIC HEALTH, INDUSTRIAL MEDICINE AND SOCIAL HYGIENT

Reports of an Influenza Type A Epidemic

G. T. Trimble (*Journal-Lancet,* 68:50, Feb. 1948) notes that in January 1947 it was evident that a type of mild influenza-like respiratory disease was occurring in local epidemic form in the midwestern and southwestern United States. In February of that year it was found that the majority of patients with upper respiratory infection admitted to the communicable disease section of the Student Health Service of the University of Missouri showed symptoms of mild influenza. The number of cases increased to epidemic proportions, a total of 880 cases being admitted to the hospital from a student body of 10,500. The chief symptoms in these cases on admission were fever, headache, malaise, cough and aching, with abrupt onset. In 20 per cent of cases, there was also sore throat, chills, and "stuffy" or running nose. In uncomplicated cases the duration of the disease did not exceed three or four days. Chemotherapy and antibiotics were not employed unless there was evidence of secondary bacterial infection. The sera of 5 patients showing the typical influenza syndrome were tested; the serum in each case was withdrawn on the day of admission and again a fortnight later. Each serum showed an increase in titer against the Weiss A and PR8A virus strains, with little or no increase against the Lee B strain. A review of the literature indicates that vaccination against influenza, types A and B, gives considerable protection against the disease, although some epidemiologists maintain that during the February to March 1947 epidemic a new strain of influenza A virus appeared against which the vaccine employed did not give a high percentage of protection. At the University of Missouri, 34.2 per cent of the student body had been immunized with a combined influenza A and B vaccine. Of 283 of the patients hospitalized with influenza, 71 per cent stated that they had not been given this vaccine, and 29 per cent that they had been given the vaccine, but some of these patients had been vaccinated within a few days of the onset of symptoms. A campus survey of 878 students showed that 9.1 per cent of students who had been given the vaccine developed influenza in the 1947 epidemic, while 17.9 per cent of those who had not been given vaccine developed the disease.

COMMENT

The short epidemic outburst is confirmation of the known behavior of Type A strains, and the percentage protection afforded is significant. From the evidence presented, there seems little reason to doubt the existence of a virus outbreak of either PR 8 or Weiss strain. Attention is merely directed to the Michigan experience during the winter of 1946-1947, when the difference between the vaccinated and non-vaccinated controls was not significant. The titer was increased in the majority of recovered cases against the PR 8 strain although the outbreak was due to a heretofore unencountered virus. ***E.G.B.***

A Schick Survey of 18,000 Naval Recruits

F. S. Cheever (*American Journal of Public Health,* 38:374, March 1948) reports a Schick test survey on naval recruits in October 1941 to January 1942; over 18,000 recruits were Schick tested. The survey was made at a time when men were being rapidly mobilized from all parts of the country and conditions in training stations were

favorable for the spread of communicable disease, especially diseases of the respiratory tract. The incidence of Schick positive tests in these recruits was 34.2 per cent. The Maloney tests were also made, and positive Maloney reactions were obtained in 24.4 per cent of those who reacted positively to the Schick test. This indicates that 1 out of 4 of the recruits with a positive Schick reaction, and therefore presumably susceptible to diphtheria, would have reacted unfavorably to injections of toxoid if a program of immunization with this agent had been found necessary. The percentage of positive Maloney reactions among those showing negative Schick reactions was 49.2 per cent. These tests were made at four Naval Training Stations; the percentage of positive reactors was much lower at Norfolk, Va. (16.6 per cent), than at Great Lakes, Ill. (47.5 per cent), Newport, R. I. (40.9 per cent) and San Diego, Calif. (32:7 per cent). A further study of the place of birth and residence in relation to the incidence of positive Schick reactions showed the incidence of positive reactions, indicating susceptibility to diphtheria, was much higher on men coming from the northern part of the United States than in those from the southern part. This may be due to the higher incidence of clinical (and presumably subclinical) diphtheria in the South in recent years; or to more vigorous campaigns for active immunization against diphtheria. The percentage of positive Schick reactions increased with age; thus there was no evidence of gradual immunization of the population by clinical or subclinical attacks of the disease between the ages of seventeen and twenty-six years. Further statistical analysis of these figures is necessary before their full significance can be determined.

Comment

It is generally agreed that preschool and school children, in view of their high susceptibility, should be immunized against diphtheria or be given a booster injection without the necessity of doing a Schick test. Unfavorable reactions as the result of diphtheria toxoid immunizations are scarce in young children; therefore, immunization with this agent may be instituted without any fear of untoward results.

In adults, however, it is a different matter. A large proportion of adults, as shown in the above abstract, is immune. Should the indication for the protection of adults against diphtheria arise, a Schick test should be performed in order to determine whether these persons fall within the small group of susceptibles. Should they prove to be Schick positive, it is further necessary to learn whether they will react unfavorably, as did nearly 25 per cent of the susceptible recruits.

The Maloney test, which determined the sensitivity of these recruits, was performed by injecting 0.1 cc. of a 1:100 dilution of diphtheria toxoid intradermally. When local reaction to this test occurs, immunization must be performed cautiously. ***E.G.B.***

Silicosis Study and Management in the Calumet Industrial Area

C. W. Rauschenbach and associates *(Industrial Medicine,* 17:1, Jan. 1948) report the use of aluminum therapy in the prevention and treatment of silicosis in two plants in the Calumet industrial area, where previous surveys and x-ray studies had shown silicosis to be an industrial hazard. The treatment is on a voluntary basis but large groups of men exposed to silica hazard have accepted treatment both prophylactically and therapeutically. The treatment is not given any person with a severe organic lesion, or those with any evidence of active tuberculosis or a secondary infection in a silicotic area. A physical examination of each man is made immediately before taking the aluminum therapy, and an x-ray study of the chest is made immediately before and within a reasonable interval after the treatment. All treatments are given by a registered nurse. The aluminum dust or oxide is inhaled by means of an inhaler with a Douglas valve that is connected by a rubber tube to a 12-liter glass bottle in which the aluminum is suspended in the air. The patient stands erect and inhales through the mouth, the nose being clamped. The initial treatment is two to three minutes, which is increased gradually to ten minutes by the eighth treatment and kept at this level for the rest of the course. The usual course is thirty to forty treatments. No toxic reactions to the aluminum have been noted; and there have been few complaints of any discomfort; some have complained of dryness of

the throat and a cough of only a few minutes' duration after a treatment. This method of therapy has been used for nearly four years. In the men who were treated when silicosis was present, the progress of the silicosis has been definitely checked; secondary infection, especially tuberculosis, occurs much less frequently than in the period before aluminum therapy was instituted. The men state that they breathe more easily, that cough and "tightness" in the chest have been much relieved, and that they "feel better." The prophylactic value of aluminum treatments is more difficult to assess accurately at this time; but the authors are of the opinion that ultimately aluminum treatment will be of the greatest value in this field.

COMMENT

If this type of aluminum therapy can be used to prevent or reduce the incidence of silicosis in industrial plants, it will be a great adjunct to the other means of preventing the disease, since even though all other precautions, such as proper local exhaust ventilation and individual dust respirators, are used properly, there is always the possibility of breakdown of equipment, or the human element creating an exposure to the disease.

E.G.B.

PEDIATRICS

Heart Disease in San Francisco School Children

S. J. Robinson and associates *(Journal of Pediatrics,* 33:49, July 1948) report that a central registry of cardiac children in the schools of San Francisco was started at the beginning of the school term in September 1946. This registry includes only those children whose cardiac status was determined during the school year of September 1946 to June 1947. The registry shows 225 children with active rheumatic fever during this period; only 28 of these were known to be recurrent cases. Including cases in which the diagnosis was in doubt, there were 245 children with active rheumatic fever. In addition there were 199 children with inactive rheumatic heart disease but showing classical signs of rheumatic valvulitis; and 234 children with potential rheumatic heart disease, i.e., known to have had rheumatic fever within the past ten years but showing no definite evidence of heart disease. There were 8 cases considered to represent rheumatic heart disease superimposed on a congenital heart lesion. There were 240 children with congenital cardiac defects, the most common lesion being the patent interventricular septal defect. The total number of children registered as having actual or potential heart disease was 1,120; the registry also shows the essential personal history of each child including convalescent care and follow-up reports. In addition a personal survey of cardiac diseases was made by the authors in 100 San Francisco schools with a total school population of approximately 57,768; only those children were examined who had been selected by a physician or a clinic, or occasionally by the school nurse, as suspected of having cardiac disease; 698 children were examined. Of the 199 children listed in the cardiac registry as having rheumatic heart disease, 111 were examined; in addition 9 cases of active rheumatic fever were found on examination of children on the suggestion of the school nurse because of suspicious symptoms, such as fatigue or pallor. These children were immediately referred for proper medical care. In 171 children with a history of rheumatic fever, no definite evidence of cardiac disease was found at this examination. There were 114 children with congenital heart lesions examined, 13 of whom were considered operable, and some have since had operation done. In 195 children examined there was no evidence of heart disease, although they had been considered "cardiac suspects." The school registry of children with cardiac disease or potential cardiac disease is of value because it provides a method of follow-up of such children to insure that they remain under medical supervision, have adequate hospital care as indicated, and are protected as far as possible against recurrent infections that are dangerous to them.

COMMENT

This report is important because through this method of school registries we are making

the proper approach to the rheumatic fever program. Only by such a registry can we expect to follow up the cases of rheumatic fever and by such a follow-up these children can be treated for their recurrences and many recurrences may be avoided by such close supervision. This is an excellent example to be followed by other city and town school departments. ***H.E.U.***

Treatment of Infantile Diarrhea with Streptomycin and an Oral Amigen Mixture

Elvira Goettsch and associates (*Pediatrics*, 2: 1, July 1948) report the use of streptomycin and an oral amigen mixture in the treatment of infantile diarrhea during 1947. In a previous severe epidemic of infantile diarrhea during March 1945, amigen had been given orally and parenterally together with other fluids intravenously as indicated, and sulfa drugs and penicillin. The corrected mortality (deaths due primarily to the diarrhea) was 7 per cent in this epidemic. In this epidemic, a predominance of *Esch. coli* was noted in bacteriological cultures from the nasopharynx and urine. During 1947 all infants with diarrhea were treated in a separate isolation ward. The amigen mixture for oral feeding contained 33 per cent dry powdered amigen, 62 per cent glucose, 5 per cent added mineral salts and vitamins B and C. It was found that this amigen mixture was well tolerated and could be used early in the course of the disease, even in the more severe cases, making prolonged intravenous feeding unnecessary. Forty-four infants were given streptomycin, and in this group there were no deaths due to the diarrhea; 36 infants were not given streptomycin and there was one death due to the diarrhea (3 per cent mortality). In some cases streptomycin was given only after the diarrhea had continued for over a week; in other cases streptomycin was given earlier in the course of the disease. In most cases, the dosage of streptomycin was 0.5 Gm. intramuscularly and 0.5 Gm by mouth daily for seven to ten days. In less severe cases, when streptomycin treatment is begun early, oral administration alone is effective. There was no evidence of toxic reactions to streptomycin in any case. The use of streptomycin and the oral amigen mixture in addition to the routine treatment previously employed definitely shortened the hospital stay, decreased the amount of intravenous therapy needed, and reduced the mortality, as compared with the hospital experience in previous years.

COMMENT

This is a rational procedure in epidemics caused by a gram-negative organism. Some credit for the success of this experiment must be given to the efficacy of high protein with amigen. ***H.E.U.***

Penicillin Treatment of Early Congelital Syphilis

Dabney Moon-Adams and Charlotte Marker (*New York State Journal of Medicine*, 48:1245, June 1, 1948) report the treatment of 69 cases of infantile congenital syphilis with penicillin. The ages of the children ranged from less than three months to three years. In infants less than four months of age the diagnosis of syphilis was not made on positive serology alone. In most cases roentgenological examination of the bones was done. In infants less than three months of age, involvement of the bones was the most common finding (78 per cent). In the older infants, anemia was the most common symptom; snuffles were present in 61 per cent and visceral involvement in 60 per cent. No treatment for syphilis had been given the mother during pregnancy in 53.6 per cent in this series. Of the 48 infants adequately followed up, 29 showed complete serologic reversal within fifteen months; and 10 showed a marked fall in titer; 5 showed no serologic change and there were 4 deaths. Omitting the 4 deaths that occurred during or shortly after treatment, the highest percentage of failures occurred in the oldest age group (between one and three years) and in those in whom the total dosage of penicillin was less than 50,000 units per kg. body weight. The highest percentage of successful results was obtained in children receiving 100,000 units or more of penicillin per Kg. body weight. On the basis of their results in this series of cases, the authors conclude that the dosage of penicillin should be at least 100,000 units per Kg. in the treatment of congenital

syphilis; and that better results are obtained by dividing the total dosage in 120 doses, given every three hours for a period of fifteen days than by giving larger amounts in a shorter period.

Plasma in the Treatment of Post-Measles Encephalitis

C. L. Thenebe (*Archives of Pediatrics* 65:302, June 1948) reports 4 cases of post-measles encephalitis treated by plasma, given intravenously. Three of the patients were children, seven and eight years of age, and one an adult twenty-six years of age. In the children, 500 cc. of plasma were given every twelve hours for five doses. Further fluid was given, if indicated, by vein or, as the patient improved, by mouth. In each case symptoms cleared up rapidly and recovery was complete. In the past twenty-six years the author has observed many fatal cases of post-measles encephalitis. The 4 cases reported in which the administration of plasma brought about "dramatic" improvement and complete recovery are too few to permit difinite conclusions to be drawn, but the results justify further trial of this method of treatment as early as possible when the diagnosis is established. It is suggested that in addition to containing measules antibodies, the plasma may supply some of the electrolyte needs of the cerebral cells.

COMMENT

This report brings up the question of the possible use of blood plasma in the treatment of measles to prevent such complications as encephalitis. In the routine use of plasma immune globulin, which has 24 times the antigen content of plasma, we have a simple and effective means of supplying measles antigen in concentrated form. Two cc. of immune globulin will almost always completely prevent measles in a child under three years of age. ***H.E.U.***

The Use of Combined Antigens in the Immunization of Infants

D. S. Fleming and associates (*Canadian Medical Association Journal*, 95:101, Aug. 1948) report the use of a combination of diphtheria toxoid, tetanus toxoid and *H. pertussis* vaccine in the immunization of infants; the average age of the infants was four months; there were no severe reactions, and such reactions as did occur were not more severe than those observed with any of these antigens used separately. Determination of the diphtheria and tetanus antitoxin content of the blood and agglutinins against pertussis before and after immunization showed that there is definite need for immunization against these infections in infancy. It was also found that response to diphtheria toxoid is definitely increased by its use in combination with pertussis vaccine and tetanus toxoid. There was also evidence that satisfactory immunization against tetanus was obtained with this combination. The immunizing efficiency of pertussis vaccine was the same when used in this mixture as when used alone. The authors are of the opinion that "public acceptance" of immunization of infants will increase if mixtures of antigens can be used.

COMMENT

The triple toxoid is in common use at the present time. We are certain of the antigen response to the tetanus and diphtheria toxoids but it will take some years and experience in epidemics of whooping cough before we can be sure of the lasting immunity of the pertussis toxoid. ***H.E.U.***

OPHTHALMOLOGY

Capillary Fragility and Cutaneous Lymphatic Flow in Relation to Systemic and Retinal Vascular Manifestations: Rutin Therapy

J. M. Donegan and W. A. Thomas (*American Journal of Ophthalmology*, 31:671, June 1948) report the determination of capillary fragility, by a modification of the method described by Wright and Lilienfeld, in 45 diabetic patients. It was found that capillary fragility was definitely increased in diabetics, and especially so in diabetics with retinopathy. In 20 patients with hytertension and arteriosclerosis, who showed varying types of retinal complications, capillary fragility was also increased. Cutaneous lymphatic flow was found to be increased in about one-third of the

patients showing increased capillary fragility; it was not increased in congestive heart failure or in the edema of nephrosis and nephritis. Rutin was given to patients showing increased capillary fragility, usually in doses of 80 to 100 mg. daily; but in resistant cases and in those in which rapid action was desirable, much larger doses were given—240, 300 or even 500 mg. daily; no ill effects were observed even when treatment was prolonged. During an acute shortage of rutin, it was found that ascorbic acid in large doses enhanced the action of rutin. In hypertensive and arteriosclerotic patients, rutin therapy resulted in definite improvement in the retinal lesions; macular edema especially responded rapidly to this treatment; Eales's disease responded favorably in 3 cases. In the diabetic patients with retinopathy, there was no improvement in vision or decrease in the retinal lesions. However, in 18 diabetic patients under treatment with rutin for ten or twelve months, there has been no further loss of vision or increase in retinopathy. In all these cases the retinopathy was marked and probably irreversible.

COMMENT

This is confirmation of the experience of the oculist who treats diabetic retinopathy. Once the retinal changes appear, progress is steady despite the good results of insulin in control of the sugar. We are too shortsighted in our consideration of the diabetic problem because not only the metabolism of the carbohydrates but also of the hydocarbons is seriously affected. It would seem that some way of restoring the impairment of fat metabolism might be found just as insulin so successfully restores the sugar metabolism. ***R.I.L.***

Sodium Sulfacetimide in Ophthalmology

L. L. Mayer *(Archives of Ophthalmology,* 39:232, February 1948) reports the use of sodium sulfacetimide in the treatment of conjunctivitis and presents a review of the literature on the use of this and other sulfa drugs for the local treatment of ocular infections. About 3,000 eyes with acute and chronic conjunctivitis have been treated by the author with a 30 per cent solution of sodium sulfacetimide (pH 7.4). In many cases of bilateral involvement, one eye was treated with the sodium sulfacetimide solution, the other eye with some other drug, such as various silver preparations, nitromersol, "optochin," or zinc sulfate. In 365 eyes from which a foreign body was removed, from the eyelids, by wiping the cornea, or by "spudding out," the 30 per cent sodium sulfacetimide solution was dropped into the eye for several days. No infection developed in any of these cases. There were no reactions to sodium sulfacetimide that could be considered as evidence of sensitivity or as an allergic reaction; 3 patients complained of a burning sensation which was so severe that the use of the drug had to be discontinued. The average mean period required for recovery was shorter with sodium sulfacetimide than with any other drug employed in the local treatment of conjunctivitis. From these results and the review of the literature, the author concludes that sodium sulfacetimide in 30 per cent solution is "an ideal antiseptic" in acute and chronic infections of the conjunctiva.

COMMENT

This is a fine demonstration of the efficacy of sulfa drops in ophthalmology. The commentator has used neoprontosil (10% sol.) in the eye prophylactically and in treating conjunctivitis and corneal ulcers. The ideal treatment of these conditions requires thorough bacteriological examinations which in actual practice may not be availble until some time after the patient is first seen. The trial and error method is not the best but may be the only practical method. Authors should impress readers with the need for adequate after care after foreign bodies have been removed. Touching of the traumatic ulcer with carbolic acid (95%), and keping the eye closed and covered until the epithelial covering is restored, with adequate instillation of a solution like that used by the writer of the article, should be a routine measure, ***R.I.L.***

Acute Central (Hypopyon) Ulcers of the Cornea

Phillips Thygeson *(California Medicine,* 69:18, July 1948) reports 50 cases of central corneal ulcers observed and treated since 1932; the condition varied in severity, but hypopyon was a characteristic fea-

ture in all but 3 cases. Scrapings from the advancing borders of the ulcer showed the causative organism in every case; the organism could be presumptively identified by the examination of these scrapings with the Gram stain, and this was confirmed in each case by culture. Pneumococcic infections predominated as 35 of the 50 cases were of this type; 6 were caused by beta hemolytic streptococci, 5 by pyocyaneus bacilli, 3 by diplobacilli (Petit type) and one by the Friedländer bacillus. Most of these cases were seen after the introduction of the sulfonamide drugs, and were treated with sulfonamides given by mouth and by topical application. Sulfadiazine was the most effective of these drugs; a powder, an ointment, or iontophoresis with the sodium salt was employed for the local application of sulfadiazine. The results obtained were definitely superior to those with older methods in the earlier cases. Only 2 cases of pneumococcic ulcers in this series have been treated with penicillin, given intramuscularly in a dosage of 20,000 units every three hours, and applied locally in the form of instillations of a solution containing 1,000 units per cc. every half hour and iontophoretic applications of the sodium salt twice a day. In both cases there was rapid healing of the lesion with minimum cicatrization. The author has as yet had no experience with streptomycin in the treatment of corneal ulcers, but believes that streptomycin may prove to be the preparation of choice in ulcers caused by pyocyaneus bacillus and the Friedländer bacillus; while penicillin may prove the preparation of choice for pneumococcic and streptococcic ulcers. A sulfa drug and penicillin may be used simultaneously with good effect.

COMMENT

This is a very fine presentation of efficacious treatment of a very serious condition with a truly scientific demonstration of the bacterial agent operating in each case. It is gratifying to note that the sulfadiazine used was successful in more than one type of infection.
R.I.L.

Pterygium: A Simple Efficient Method of Treatment

H. G. Bullwinkle *(United States Naval Medical Bulletin,* 48:395, May-June 1948) reports the use of Kamel's operation in the treatment of pterygium. Operation may be done at once in cases in the atrophic stage; in cases in the progressive stage, the eye is treated for about two weks with cleansing, soothing drops and ointments before operation. At operation, after insertion of the speculum, the neck of the pterygium over the limbus is picked up with fixation forceps, and the head of the pterygium is shaved from its corneal attachment. The pterygium is then well undermined to the caruncle, using fine strabismus scissors, the fold of undermined tissue is raised from the sclera, and its undersurface is cauterized with carbolic acid, using a wooden toothpick. This tissue, when phenolized, dries almost immediately so that it can be replaced without injury to the sclera. At the end of the operation a small amount of a mild ophthalmic ointment is placed in the lower cul-de-sac; the eye is dressed daily with ½ per cent zinc sulfate eye drops and the ointment for fourteen to twenty-four days; but a bandage is worn for only four or five days. The author became interested in the study of pterygium while on duty in American Samoa, where the condition is frequent among the natives, and almost invariably recurs after the usual methods of treatment. He is of the opinion that if Kamel's method of treatment had been known and tried at that time, results would have been better. In the cases of pterygium since treated in the United States by Kamel's method, results have been excellent, with no recurrence. It is a simple operation that can be done by any medical officer in the Service on shipboard or in isolated outposts where trained ophthalmologists are not available.

COMMENT

The average oculist practicing in a city cannot have an accurate conception of the seriousness of this condition and its tendency to recurrence which suggests a malignancy, as so often seen in China and the tropics. The usual transplant of the advancing head is very effective in this country but some of the cases from China and the Mediterraneum have been amenable to nothing short of replacing the diseased tissue with buccal mucous membrane. A simple method that can be used by the

average medical attendant may eliminate many cases in the early stages. ***R.I.L.***

Fat Embolization Involving the Human Eye

M. H. Fritz and M. J. Hogan *(American Journal of Ophthalmology,* 31:527, May 1948) report a case in which fat embolization involved the eye. The patient was a soldier who had been injured in an explosion of a gasoline stove and showed multiple fractures and severe shock. When the patient's general condition improved under treatment for shock, operation was done for reduction of the fractures. On the following day, the patient became unconscious and coma persisted until death. From the history, symptoms, and the finding of fat in the urine, a diagnosis of fat embolization was made. Eye-ground examination showed round and oval, white subretinal exudates surrounding both maculae and following the course of the retinal vessels; the diagnosis was multiple fat emboli of the retinal vessels, with secondary edema of the retina. At autopsy, sections from both eyes showed fat emboli in the terminal arterioles and in the capillaries of the retina, with edema and degeneration of the retina in the region of these emboli, probably due to lack of nutrition caused by the blockage of these blood vessels. The larger blood vessels of the retina and the optic nerve showed no emboli. A review of the literature shows only one other case in which the ocular findings in fat embolization are reported; this was also a case of multiple fractures. In this case, the patient recovered, and the diagnosis of ocular fat emboli was based on the ophthalmoscopic findings. The authors' case is reported because of "the paucity of information" in regard to ocular complications of generalized fat embolization, and the definite findings in their case.

Comment

This is a very fine observation of a very rare condition. One cannot but think that the so-called "Berlin's edema of the retina" occurring after trauma with chest compression (as in overturned autos with the driver caught behind the wheel) may be somewhat similar. ***R.I.L.***

HYPOPROTHROMBINEMIA

—Concluded from page 497

1947 the bromsulfalein test showed no retention of dye after 30 minutes; on March 14, 1947, the prothrombin was 92.2% of normal. On March 15, 1947, the urine was negative throughout.

While in the hospital, the patient had an electrocardiogram and x-ray studies of the chest and gastro-intestinal tract. The only unusual finding was of a long, right-sided sigmoid and a high cecum which lay beneath the liver.

This patient has been followed since. He continues to do as he did before, which included the imbibing of a moderate amount of alcoholic beverages. He refrains, however, from taking aspirin, and has had no recurrence of bleeding. On April 22, 1947, his studies showed Hb. 82%, red blood count 4,380,000, white count 9,650, normal differential, coagulation time 3½ minutes, platelets 280,000, clot retraction one hour, serology negative.

This case is reported because of the effect of aspirin on the prothrombin, leading to extensive hemorrhage into the skin and mucous membranes. The tendency for the platelets to drop may or may not be part of the etiology. Because of this effect of aspirin, one believes it should be used with caution postoperatively, should be suspected as a possible cause for hemorrhage of unknown etiology, and should be studied so that it can possibly be used with advantage where thrombosis is occurring or imminent as in coronary artery disease.

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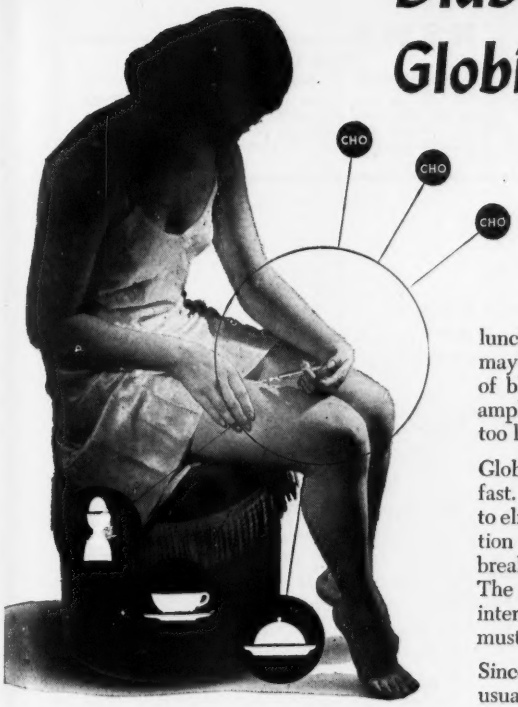
Diabetes, diet and Globin Insulin . . .



THE ADVANTAGES of one-injection control of diabetes can, through adjustment of diet and dosage, be made available to the majority of patients requiring insulin. In view of the convenience and freedom afforded by the unique intermediate action of 'Wellcome' Globin Insulin with Zinc, the necessary adjustment is well worth while. Though not a complicated procedure, the regulation of carbohydrate balance warrants reiteration because of its importance:

SOME FACTS ABOUT DIETARY ADJUSTMENT: The distribution of carbohydrate in the meals must be adjusted in accord with the type of action exhibited by Globin Insulin, which is intermediate between regular and protamine zinc insulin. Proper carbohydrate distribution with proper insulin timing is essential; lack of balance may lead to poor control or to an erroneous impression of the characteristics of Globin Insulin.

A good carbohydrate distribution for the patient on Globin Insulin is to divide the total carbohydrate per day into 1/5 at breakfast, 2/5 at lunch and 2/5 at suppertime. This initial diet may be adjusted in accord with the indications of blood sugar levels and urinalyses. (For example, a low blood sugar before supper indicates too little carbohydrate for lunch or vice versa.)

Globin Insulin is ordinarily given before breakfast. Onset of action is usually sufficiently rapid to eliminate the need for a supplementary injection of regular insulin. However, the amount of breakfast carbohydrate should not be too large. The right amount, as well as the optimal time interval between the injection and breakfast, must of course be determined for each patient.

Since the maximum action of Globin Insulin usually occurs in the afternoon or early evening, hypoglycemia is sometimes noted at this time. As a guard against it, the carbohydrate content of the noon meal may be increased, or a midafternoon lunch provided. Thus the original distribution of 1/5, 2/5 and 2/5 might, for example, require adjustment to 2/10, 5/10 and 3/10 or to 2/10, 4/10, 1/10 and 3/10. Once the balance of carbohydrate intake and insulin timing has been established, the patient must be impressed with the importance of adhering to the regimen.

'Wellcome' Globin Insulin with Zinc is a clear solution, comparable to regular insulin in its freedom from allergenic properties. Available in 40 and 80 units per cc., vials of 10 cc. Accepted by the Council on Pharmacy and Chemistry, American Medical Association. Developed in The Wellcome Research Laboratories, Tuckahoe, New York. U.S. Patent No. 2,161,198. LITERATURE ON REQUEST.

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SIR JAMES PAGET
1814–1899

Classical Quotations

● Soon after the beginning of her pain, that is, about ten or twelve years ago, her daughters thought that she was losing in height, and that the shape of her head was changing; and from that time she had been becoming less tall, till now she had lost four inches and a half in height, and stooped so low with her head forward and her chin raised.

SIR JAMES PAGET
Additional Cases of Osteitis Deformans, Med. Chir. Trans. London 1882, 65:225.

Pediatrics

Advances in Pediatrics. Editorial Board, S. Z. Levine, M.D., Allan M. Butler, M.D., L. Emmett Holt, Jr., M.D., & A. Ashley Weech, M.D. Vol. 2. New York, Interscience Publishers, [c. 1947]. 8vo. 409 pages, illustrated. Cloth, $6.75.

The second volume of *Advances in Pediatrics* sets a high standard. Both the Pediatrician and the General Practitioner will find a wealth of practical material for diagnosis and treatment and the research worker will revel in the neat, orderly, and systematic presentation and the critical evaluation of a vast amount of clinical and experimental data. The articles are uniformly complete, comprehensive, critical, and authoritative. No doubt, both editors and contributors worked hard to attain this goal. In doing so they made the task of the student, the clinician, the teacher, the research worker, in fact anyone who desires to keep step with progress in pediatrics, a very pleasant one.

BENJAMIN KRAMER

Cerebral Localization

Trastornos Psiquicos en Traumatisados Craneales. By Dr. Vallejo Nagera & Dr. Escudero Valverde. Barcelona, J. M. Massó, [c. 1947]. 8vo. 159 pages. Paper, 30 ptas. (Estudios Monograficos de Investigacion Medica.)

In this monograph the authors revive the theory that the familiar doctrine of cerebral localization be extended to include definite "centers" for psychic or personality traits. These centers need not have "topographic" or "geometric" limits as suggested by the older writers, e.g., Gall, Bowers, Flourens, but they may be a group of nervous elements banded together functionally for a certain type of activity. In order to explain the diversity of symptoms both neurological and psychological, induced by cerebral injuries, the "dynamic theory" of Gonzalo is offered, which states that, following violent trauma, not only the injured area is disturbed in function, but the entire brain reacts as a unit, causing diffuse alterations in cerebral activity.

A bibliography is provided but there is no index.

DENNIS RYAN GILLEN

Long Bone Surgery

Osteotomy of the Long Bones. By Henry Milch, M.D. Springfield, Illinois, Charles C Thomas, [c. 1947]. 8vo. 294 pages, illustrated. Cloth, $6.75.

This book describes osteotomies of all types which can be done on long bones. The text is excellent if one has the endurance to read through page after page of mathematics. The book is useful for reference. It should be re-written so that it can be read without bewilderment.

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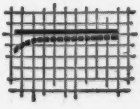

a titration curve comparable to that of fresh milk.

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Habitual Drinking Cure

If A Man Be Mad. By Harold Maine. Garden City, N. Y., Doubleday & Co., [c. 1947]. 8vo. 435 pages. Cloth, $3.00.

The story is taken from the writer's own experience. In his attempt to find a cure for his "drinking," he utilizes the services of office psychiatry, Alcoholics Anonymous, and mental institutions, with little or no success. He then becomes an attendant in a V. A. Psychiatric Hospital, and finally loses his desire for drink through his effort to help other unfortunate individuals afflicted with more severe forms of psychoses.

The book is well written and boldly exposes many of the abuses which previously existed in mental hospitals.

WILLIAM E. MCCULLOUGH

First Aid Treatment

First Aid Surgical and Medical. By Warren H. Cole, M.D., & Col. Charles B. Puestow, M.C., A.U.S. Illustrated by Carl Linden in collaboration with Tom Jones. 3rd Edition. New York, D. Appleton-Century Co., [c. 1946]. 8vo. 351 pages, illustrated. Cloth, $3.00.

Although it is ideal to have all first aid administered by physicians, this is not always possible. It is, therefore, necessary to train certain members of the lay group to act intelligently and efficiently during an emergency. In view of the fact that the subject of First Aid should be a part of the curriculum in medical schools, the authors of this book have made it sufficiently simple so that the lay individual can understand it and can use it as a guide, but it is also written in a sufficiently scientific manner so that it may be used as a basis for instruction in first aid in medical schools, as well as a reference book for physicians, who are in general practice but who may be called upon to administer first aid treatment.

Because the administration of antibiotic drugs, blood, and plasma now plays an important role in modern first aid care, their use has been properly discussed in the text.

The book is recommended to industry, to medical schools, and to the general practitioner.

MERRILL N. FOOTE

Biochemistry

Biochemistry for Medical Students. By William Veale Thorpe, Ph.D. 4th edition. Baltimore, Williams & Wilkins Co., [c. 1947]. 8vo. 496 pages, illustrated. Cloth, $5.00.

This is a text book of Biochemistry for Medical Students and has been a standard for a decade. This is the fourth edition and has been brought up to date as far as is practicable in our rapidly expanding knowledge of Biochemistry.

MORRIS ANT

The Anemias

L'Anemie Infectieuse. By G. Hemmeler. Basel, Switzerland, Benno Schwabe & Co., 1946. 8vo. 76 pages, illustrated. Paper, 5 Swiss fr.

This is an excellent monograph presenting the results of careful study of the anemias resulting from typhoid fever, undulant fever, subacute bacterial endocarditis, acute poly-arthritis, tuberculous meningitis and miliary tuberculosis. The author studied the reticulocytes and bone marrow as well as the red cells and found that infectious anemias are isochromatic and aplastic. Blood regeneration is therefore diminished and since hemolysis is greater than normal an anemia results. Iron and liver extracts are of little value in treatment. Transfusions are useful.

EDWIN P. MAYNARD, JR.

New Edition of Dorland

The American Illustrated Medical Dictionary. A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, Etc., with the Pronunciation, Derivation, and Definition. By Lt. Col. W. A. Newman Dorland, M.R.C. (USA). With the collaboration of E. C. L. Miller, M.D. 21st Edition. Philadelphia, W. B. Saunders Company, [c. 1947]. 8vo. 1,660 pages, illustrated. Flexible Cloth, $8.00. With Thumb Index, $8.50.

This twenty-first edition of Dorland's *Dictionary* reflects the great progress of medicine during the war years; the voluminous additions, indeed, in large part represent the research and discovery in the actual field of war medicine and surgery. The medical applications of radioactive isotopes, for example, occasion notable enrichment of our terminology.

We note the change from co-ca-in to co-cain, with pto-ma-in and co-ma-ine retaining the old division of their syllables.

ARTHUR C. JACOBSON